Thomas A. Ban, Eric Konofal and Andrew Winokur: Historical Drug Inventory of Psychotropic Drugs

Collated by Olaf Fjetland

This Collated Document is comprised of four entries including the Introduction, followed by two vignettes, one on Bromides and the other on methylphenidate, and one essay on the thyrotropin releasing hormone. Three authors contributed postings: two by Eric Konofal and one each by Thomas A. Ban and Andrew Winokur. The first entry was made on June 30, 2013, and the last on December 19, 2015.

This collated document is now open to all INHN Members for final comments.

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Eric Konofal: Introduction

I am writing to introduce myself as the person responsible for the project "Historical Drug Inventory on Psychotropic Drugs" (Project 2). I will be working on this project with Tom Ban, Barry Blackwell, Sam Gershon and Peter Martin in preparing vignettes on psychotropic drugs for inclusion in our Inventory and editing vignettes prepared by others.

We hope you will be interested in participating in this project by preparing vignettes for our Inventory and commenting on vignettes already included in it.

I am posting with this Introduction a vignette on "Methylphenidate" I prepared.

I am looking forward to working with you on this project.

June 27, 2013

Eric Konofal: Methylphenidate

The story of methylphenidate begins with the recognition that piperazine derivatives, used as diuretics in the late 19th century possessed significant stimulating properties.

Chemische Industrie Basel (CIBA) is a Swiss pharmaceutical company where Max Hartmann, a chemist, in the early 20th century synthesized a piperidine, allyl-phenyl-cinchoninate, a powerful treatment for "uric acid diathesis." Hartmann continued his research with piperidines and, in 1924, synthesized N-diethyl-3-pyridine carboxamide, a strong analeptic that was to be called nikethamide or picolinamide. With Werner Boshard, Hartmann published, in 1941, an article on pyridine-3-acetic acid. Three years later, subsequent transformations and reductions of some pyridil acetic acids, led to the isolation of phenyl-α-pyridil-2-acetic acid. Leandro Panizzon (1944), a medicinal chemist at CIBA, lead the synthesis of methyl-α-phenyl-piperidine-2-acetate (methylphenidate).

In 1950, Panizzon and Hartmann developed an improved synthesis for methylphenidate and obtained a US patent for its preparation. However, it was only, in 1954, that Meier, Gross and Tripod revealed that this substance has stimulating properties. In the same year, methylphenidate, with the brand name Ritalin, was patented by CIBA in the US for treating psychological disorders. By 1955, Ritalin passed the safety requirements of the US Food and Drug Administration in effect at the time, and in 1956, it was introduced for clinical use. In 1957, it was marketed in Europe to treat fatigue, psychasthenia or depression.

The substance was first used intravenously for the treatment of barbiturate intoxication (Rosenberg, Rape and Rumble, 1959), but by the end of the 1950s, it found its place in the treatment of narcolepsy (Yoss and Daly, 1959) and in "some abnormal psychical conditions," primarily, in a disorder that was first described by English physician George Frederic Still, in 1902, and was to be first referred to as "minimal brain dysfunction," and subsequently "attention deficit hyperactivity disorder" (Lytton and Knobel, 1959).

The overall clinical profile of methylphenidate resembles that of amphetamine, with the exception that its anorexic effects and actions on the peripheral circulation are less marked. It acts by inhibiting dopamine reuptake and with much less effect on norepinephrine reuptake (Findling, 2008).

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June 27, 2013

Thomas A. Ban: Bromides

Potassium bromide was the first widely used sedative in medicine. It is the potassium salt of bromine, the element that was named for its “stench” (“bromos”).

Bromine was first isolated in 1826 from the ashes of seaweed by A.J Balard, an apothecary in Montpelier, France. He found bromine in its natural form too corrosive for ingestion and prepared for clinical use the potassium and sodium salts of the substance (Shorter, 1997).

Bromine was introduced into medical practice by François Magendie in Bordeaux (France) and subsequently, in the 1830s and '40s, bromide was extensively used as a substitute for iodine in a variety of disorders (Garrison, 1960). It was only in the mid-1850s that Charles Lockock, a London internist, discovered the anticonvulsant property and sedative action of the drug. It was one of the many quaint examples of serendipity in which a false theory led to correct empirical results. Lockock, like many physicians in his time, believed that convulsions and epilepsy were caused by masturbation and since bromides were known to curb sex drive, he administered potassium bromide with the rationale that by reducing the frequency of masturbation he will be able to control epileptic seizures (convulsions) in his patient (Lehmann and Ban, 1970). The treatment was a success insofar as control of convulsions was concerned. It also focused attention on the sedating properties of the drug (Ban, 2006).

During the second half of the 19th century, potassium bromide was widely used for sedation and for the control of anxiety and convulsions (Balme, 1976). In 1900, Neil Macleod, a Scottish physician, reported on "bromide sleep" in the treatment of acute mania. Yet, the bromides were difficult drugs to use. Since they act by replacing chlorides, their activity depends not only on the amount of bromide given, but also on the chloride intake, fluid consumption and renal function of the patient. The problem is compounded by its slow excretion and rapid accumulation in the blood. The earliest manifestations of bromide intoxication are sleepiness and fatigue; and as blood-concentrations increase appetite is lost, weight decreases and a characteristic mental dullness appears. A toxic delirium is triggered when bromide levels pass a critical threshold (Ban, 1969).

In one particular aspect, the bromides differ from all other sedatives: they don't induce drowsiness and sleep when given in a large single dose. Nevertheless, because of their relatively low efficacy coupled with high toxicity the use of bromides was virtually restricted for controlling seizures in pediatrics by the late 1960s (Ban, 2006).

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October 24, 2013

Andrew Winokur: Thyrotropin releasing hormone (TRH)

Thyrotropin releasing hormone (TRH) was isolated and characterized, in 1969, as a tripeptide pyroglutamyl-histidyl-proline amide (Boler et al., 1969; Burgus et al., 1969). TRH was the first of the hypothalamic releasing hormones to be isolated and characterized. This event represented one of the landmark scientific accomplishments of the 20th Century, and the two investigators who are most credited with carrying out this groundbreaking work, Roger Guillemin and Andrew Schally, shared the Nobel Prize in 1977 for this achievement. Work leading to the identification of the hypothalamic releasing hormones was carried out over a 20-year research effort marked by intense competition between Guillemin's and Schally's groups. The foundation for this remarkable effort was developed by the contributions of investigators during the previous half century, but it required the paradigm-shifting innovations of Guillemin's group and Schally's group to bring this massive research effort to the point of ultimate success. At that time, many prominent scientists were highly skeptical of the existence of the hypothalamic releasing hormones, and the National Institutes of Health (NIH), after years of heavily funding the work in both investigators' laboratories actually convened a special meeting, in 1966, to consider whether funding for this project should be halted in light of questions about the likelihood of success. A three-part series in SCIENCE in 1978 thoroughly describes the background and circumstances related to the discovery of TRH and other hypothalamic releasing hormones, as well as describing the unique relationship between the two lead investigators (Wade, 1978).

As noted above, the discovery of TRH as the first identified hypothalamic releasing hormone was a truly transformative development for the field of Endocrinology. This discovery provided explicit demonstration of the manner in which the brain plays an intimate, pivotal role in the regulation of peripheral endocrine function through regulation of the synthesis and section of hormones released from the anterior pituitary gland (Jackson, 1982). It was now established that hormones were secreted directly from the brain, in contrast to the previously identified circumstance in which the hormones oxytocin and vasopressin were synthesized in the hypothalamus but then transported down neural pathways to the posterior pituitary gland, to be stored until being secreted from that site in the periphery into the general circulation. In the case of TRH, it is synthesized in hypothalamic neurons, transported to the presynaptic terminal region in the median eminence, where it is stored in synaptic vesicles. With firing of an action potential, the TRH neurons in this region release their vesicle contents in the portal circulation, from whence it diffuses directly to the anterior pituitary gland and is bound to TRH receptors on thyrotroph cells, leading to increased synthesis and secretion of thyrotropin (TSH) into the general circulation. In turn, TSH acts on the thyroid gland to stimulate synthesis and secretion of the thyroid hormones, in particular T4, which is then mainly enzymatically converted extrathyroidally to the more active form, T3. In turn, feedback inhibitory loops were demonstrated that involved effects of the thyroid hormones on both the anterior pituitary gland and back in the brain at the level of the hypothalamus. Thus, with TRH and the hypothalamic-pituitary-thyroid axis serving as the originally identified example of a neuroendocrine axis, the bidirectional relationship between brain and endocrine function was firmly established.

TRH has clearly been established to be the primary regulatory factor in the normal function of the thyroid axis. Hypothalamic hypothyroidism was identified as a condition in which patients developed hypothyroidism secondary to inadequate secretion of TRH from the hypothalamus. By 1972, parameters for the “TRH stimulation test” had been published, and this procedure became a standard, widely utilized diagnostic procedure to evaluate the appropriateness of the TSH response and to aid in the diagnosis of selected thyroid disorders (Snyder and Utiger, 1972). In the TRH stimulation test, an indwelling cannula is placed in a vein, and plasma samples are obtained to determine the baseline TSH concentration. TRH, usually at a dose of 400-500 micrograms to obtain a maximal TSH response, is then injected intravenously, typically as a bolus injection or infused over 30 seconds. Blood samples are

obtained at 10-15-minute intervals up to 60 minutes or longer following administration of TRH, and the increase in TSH concentration over the baseline value is determined. The peak TSH value after TRH administration is typically seen 30 minutes after TRH administration, and TSH levels typically return to baseline values by 60 minutes. Normative values for the TSH response to TRH have been established, and results from patients with suspected thyroid disorder can be described as blunted, normal or exaggerated. By the mid-1990's, the availability of ultra-sensitive radioimmunoassay procedures for TSH made the TRH stimulation test an unnecessary diagnostic procedure in the view of many endocrinologists, and the use of the TRH stimulation test for diagnostic purposes in the U.S. markedly waned. As noted in an editorial in THYROID, TRH has not been available in the U.S. since 2002, as Ferring Pharmaceuticals, the only supplier of TRH in the U.S., was required to remove their TRH product (Thyrel) from the market due to questions on the part of the FDA regarding their production processes (Rapaport et al., 2010). The editorial noted above was entitled "Time for Thyrotropin Releasing Hormone to Return to the United States of America." The authors of this editorial argued that there are still instances in which the use of the TRH stimulation test is important to diagnosis certain forms of thyroid disease states. Nonetheless, clinical grade TRH remains commercially unavailable in the U.S.

How did TRH attract the interest of some psychiatric investigators? Suggestions regarding a relationship between thyroid axis function and mood disorders had been expressed many years before the discovery of TRH. Notably, Prange et al. (1969) reported that administration of small doses of triiodothyronine (T3) to depressed patients, in conjunction with standard treatment with a tricyclic antidepressant drug, resulted in a more rapid onset of antidepressant activity. Additionally, Schildkraut et al. (1970) reported that addition of a low dose of thyroid hormone to a 10-day tricyclic antidepressant drug regimen produced an acceleration of norepinephrine turnover in rat brain. With the availability of TRH for experimentation purposes, it is not surprising that investigators rapidly examined the effects of TRH in various animal behavioral paradigms. In 1972, only three years after its discovery, TRH was reported to be active in the DOPA potentiation test of Everett, a putative animal model screen for drugs with antidepressant effects (Plotnikoff et al. 1972). The investigators examined the effects of TRH administered to groups of rats with partial or complete ablation of the peripheral thyroid axis (i.e., rats who had been hypophysectomized, thyroidectomized or both hypophysectomized and thyroidectomized prior to administration of TRH) (Plotnikoff et al.

1974). In the surgically ablated rats, administration of TRH demonstrated full behavioral activity in the DOPA potentiation test. The results of these studies suggested that: 1) TRH administration would be associated with antidepressant activity, and 2) effects of TRH in the DOPA potentiation test were independent of the effects of TRH on the thyroid axis and likely represented direct CNS effects.

Prange et al. (1972) and Kastin et al. (1972) administered TRH or saline intravenously (i.v.) to depressed patients, and both groups reported significant improvement in symptoms of depression following administration of TRH. A notable feature reported in both studies was the finding that improvement in symptoms of depression occurred literally within hours of administration of TRH, a striking contrast to the well-established finding that the standard antidepressant drugs of the time, the tricyclic antidepressant compounds and the monoamine oxidase inhibitor antidepressants, typically took several weeks to achieve therapeutic effect. At the present time, there is a high degree of interest in the observation that administration of i.v. ketamine produces rapid improvement in depressive symptoms, a finding that may lead to significant advances in the pharmacotherapy of some forms of depression. In this context, it is interesting to note that rapid improvement following i.v. administration of TRH was first reported some four decades ago. A study of the effects of TRH administration to depressed patients by Itil et al. (1975) included both clinical assessments and evaluation by means of computed EEG analysis. Not only were depressed patients noted to demonstrate symptomatic improvement in this study, but EEG evaluation 24 hours after infusion of a single dose of TRH was reported to produce an activation of the computed EEG profile that was comparable to effects produced by stimulant compounds such as dextroamphetamine, as well as by the monoamine oxidase inhibitor tranylcypromine. Overall, with respect to the efficacy of i.v. TRH in controlled studies involving depressed patients, only about 42% of studies demonstrated efficacy associated with TRH administration as compared to placebo or to treatment with a tricyclic antidepressant compound (Prange et al., 1979). Variation in experimental design and in the characteristics of patients enrolled may account for some of the inconsistency in results reported in studies with TRH. Clearly, further studies are needed to more critically evaluate the therapeutic potential for TRH or a TRH analog in the treatment of depression.

The reports of Prange et al. (1972) and Kastin et al. (1972) included the additional observation that a subset of depressed patients demonstrated an inadequate or “blunted” TSH

response to TRH administration. Over the years, dozens of studies have replicated the finding of a blunted TSH response to TRH in subsets of depressed patients (typically on the order of 25% of patients examined) (Loosen and Prange, 1982). Suggestions about the significance of this blunted TSH response have included potential utility in diagnosing depression, prediction of treatment response or providing an indication of the risk for relapse after treatment has been terminated and the possibility that this finding may provide insight to pathophysiological mechanisms of relevance to depression (Loosen, 1985; Kirkegaard et al., 1975; Banki et al., 1988). As noted above, TRH has not been available for clinical use in the U.S. since 2002, and as a consequence, the TRH stimulation test can no longer be employed for clinical studies in the U.S. In light of these circumstances, it does not seem likely that further studies investigating the relevance of the TRH stimulation test for patients with depression will be carried out in the U.S.

Studies examining the role of TRH in the central nervous system (CNS) have been pursued over the past 4 decades, and advances in this area offer the promise of enabling new approaches to clinical translational studies involving TRH or TRH analogs. Utilizing, at the time, a recently developed radioimmunoassay technique for TRH, Winokur and Utiger (1974) and Jackson and Reichlin (1974) reported on the widespread distribution of this "hypothalamic releasing hormone" throughout the rat brain. The hypothalamus was found to contain only one-third of the TRH content in the rat brain. The widespread distribution of TRH in the CNS, combined with previously reported behavioral effects associated with TRH administration provided a solid rationale to undertake further studies to elucidate the role of this tripeptide in the CNS, in addition to its established hypothalamic hypophysiotropic function. Specifically, studies were undertaken to examine the possibility that TRH plays a role as a neurotransmitter in the CNS. Findings that support a neurotransmitter role for TRH include: 1) the identification of the pre-pro-TRH gene and the pre-pro-TRH peptide in neurons throughout the CNS (Nillni and Sevarino, 1999); 2) the presence of TRH in synaptic vesicles in the presynaptic neuron in both hypothalamic and extra-hypothalamic brain tissue (Winokur et al., 1977); 3) the presence of TRH receptors in high concentration in specific locations throughout the neuroaxis in lower species and in man (Manaker et al., 1985; Manaker et al., 1986); 4) the presence in the CNS of mechanisms to terminate the effects of released TRH by peptidases located in various brain regions, including a deamidating enzyme and two species of pyroglutamyl-amino-peptidases, (Torres et al., 1986; Hersh and McKelvy, 1979); 5) demonstration of the ability of TRH to

produce alterations in neuronal membrane conductance by means of intracellular recording techniques, as well as studies employing unit recording of actively firing neurons both in the hypothalamus and in other brain regions that demonstrated alteration in neuronal firing rate following administration of TRH by microiontophoresis (Winokur and Beckman, 1978); and 6) demonstration of an array of physiological and behavioral effects associated with administration of TRH and TRH analogs in preclinical animal studies and in studies involving human subjects, as will be discussed in more detail below.

Animals pretreated with a variety of CNS depressant compounds, including ethanol, barbiturates, other anesthetic agents, or antipsychotic drugs that are then administered TRH demonstrate a significant shortening of sleeping time and a reversal of hypothermia induced by pharmacological treatment with a CNS depressant agent (Breese et al., 1975). This remarkable and unique analeptic action of TRH appears to represent a distinctive property of the tripeptide. Stanton et al. (1980) examined effects of TRH in a natural state of CNS depression, i.e., hibernation in the California golden-mantled ground squirrel. Administration of TRH to the hibernating ground squirrel produced a pronounced increase in brain temperature and metabolic rate, and within one to two hours following administration of TRH, ground squirrels demonstrated full behavioral arousal from hibernation. Arousal from hibernation was seen when TRH was administered into the CA1 region of the dorsal hippocampus of the hibernating ground squirrel, a region subsequently demonstrated to contain a high concentration of TRH receptors in this species. TRH is highly potent in producing this effect, as doses as low as 100 picograms resulted in full behavioral arousal from hibernation. However, the response was strictly dependent on providing the precise molecular structure of TRH, as administration of the deamidated free-acid form of TRH (TRH-OH) in much higher concentration was completely devoid of physiological effects.

Stanton et al. (1981) extended studies of effects of TRH by microinjecting TRH into the same location (i.e., dorsal hippocampus) in ground squirrels that were euthermic and in the state of slow wave sleep. In this instance, administration of TRH produced effects that were similar in direction, but smaller in magnitude than the effects observed in the hibernating ground squirrel. Thus, administration of TRH to grounds squirrels during slow wave sleep resulted in a modest increase in brain temperature and metabolic rate, and a slight activation of EEG pattern and increase in EMG activity, although the animals did not exhibit full behavioral arousal. In

contrast, when TRH was administered in the same paradigm to ground squirrels that were euthermic and awake, the effects observed were OPPOSITE in direction to the effects seen in the hibernating and in the euthermic sleeping ground squirrels, including a decrease in brain temperature and metabolic rate, a slowing of the EEG pattern and a decrease in EMG activity. When TRH was administered to ground squirrels that were behaviorally active, a readily evident reduction in motor activity was observed. The results obtained in this series of studies prompted the investigators to speculate that TRH plays a key role in the bimodal regulation of arousal.

Additional studies have examined the relationship between TRH and CNS activity states. Determination of TRH and TRH receptor concentrations in brain regions of ground squirrels sacrificed during different seasons demonstrated significant variations in both the tripeptide and its receptor in selected brain regions as a function of season (Stanton et al., 1982). The concentration of TRH in the hypothalamus of hibernating ground squirrels was significantly lower than that in euthermic ground squirrels sacrificed in the winter. Studies were conducted in another animal species that undergoes a state of profound CNS torpor, namely the South African lungfish, which enters a state of estivation during the summer dry season in its natural habitat (Kreider et al., 1990). Estivating lungfish studied in the laboratory demonstrated a significant reduction in TRH content in the diencephalic region (a region containing the hypothalamus) as compared to awake control lungfish, a finding comparable to the reduced hypothalamic TRH content previously reported in hibernating ground squirrels.

The primary approach to examining the relationship between TRH and CNS hyperarousal has been by means of experimental seizure induction. Studies utilizing a variety of seizure-induction paradigms, including electroconvulsive shock, kainic acid-induced seizures and amygdala-kindled seizures have all reported pronounced increases in TRH content in limbic regions, including amygdala, entorhinal cortex and hippocampus (Kubek et al., 1989; Kreider et al., 1990; Post and Weiss, 1992). It has been speculated that the increase of TRH content provoked by experimental seizure-induction procedures unmasks an endogenous compensatory response to modulate excessive seizure activity, with TRH being a prime candidate to mediate the compensatory response to oppose seizure activity (Post and Weiss, 1992). When TRH or TRH analogs have been administered in a variety of seizure-induction paradigms, a reduction in seizure activity has consistently been reported. Moreover, limited studies in humans with

various forms of intractable seizures have reported that administration of TRH or TRH analogs is associated with anticonvulsant effects.

Based on the types of observations summarized above, the TRH Hypothesis of Homeostatic Regulation was proposed, suggesting that TRH neuronal systems in the CNS play a key role in maintaining activity within a regulated range (Gary et al., 2003). Moreover, administration of TRH during states of CNS hypoarousal (e.g., hibernation in the ground squirrel) would lead to an increase in CNS activity, whereas administration of TRH during a state of hyperarousal (e.g., seizure activity) would lead to a reduction towards normal of the hyperarousal state. Based on this theoretical construct, a number of therapeutic applications for TRH and TRH analogs were proposed.

A few selected examples of translational research studies involving TRH will now be discussed. Nishino et al. (1997) administered TRH and the TRH analog CG-3703 (Grunenthal GmbH) in the canine narcolepsy model. Administration of both TRH and CG-3703 produced a statistically significant increase in wake time (i.e., a reduction in hypersomnolence) and a dose-dependent decrease in episodes of cataplexy in the narcoleptic dogs.

Szuba et al. (2005) administered TRH or saline in random order to bipolar patients who were studied during an episode of depression and examined behavioral responses during the next 48 hours. A substantial and statistically significant reduction in physician-evaluated depression scores was observed as soon as 9 hours after administration of TRH, with the improvement being sustained throughout the 48-hour observation period. This finding was consistent with the rapid improvement in symptoms of depression following administration of TRH that was originally reported by Prange et al. (1972). Data were also collected by means of the Profiles of Moods States (POMS) questionnaire. The use of the POMS provided access to several dimensions of physical and emotional symptom ratings by means of validated POMS subscales. Significant improvement was observed in bipolar patients who were randomized to receive an infusion of TRH on the depression, anxiety, mental confusion, fatigue and vigor subscales. Particular emphasis is drawn to the results on the fatigue subscale, which demonstrated that significant improvement in fatigue ratings was noted on the first day after TRH administration, but even greater improvement in fatigue ratings was observed on the second day after TRH administration. In bipolar patients, episodes of depression are particularly associated with

symptoms of hypersomnolence, apathy, lethargy and fatigue. TRH or a TRH analog may present a novel treatment for bipolar depression, a condition for which a limited number of approved, effective treatments are available.

As noted above, the TRH Hypothesis of Homeostatic Regulation suggests that administration of TRH during a state of CNS hypoarousal would result in an increase in the arousal level to an optimal range of activity. The study of Szuba et al. (2005) identified pronounced improvement in ratings of Fatigue on the POMS subscale in patients with bipolar depression. Kamath et al. (2012) conducted a clinical study to examine the therapeutic value of TRH in patients with cancer who were suffering with prominent fatigue symptoms. In an NIH "State of the Science Symposium" report, fatigue was cited as the most prevalent and most disabling symptom afflicting cancer survivors (National Institute of Health State of the Science Panel, 2003). In the study of Kamath et al. (2012), cancer patients were studied in a crossover design in which each subject received two infusions of TRH and two infusions of saline placebo a week apart in each case. Administration of TRH resulted in a pronounced and statistically significant increase in ratings of energy on a visual analog scale, with improvement in energy initially reported 8 hours after infusion of TRH and significant, persistent improvement in energy ratings being evident for 72 hours after a single TRH infusion. The estimated effect size (Cohen's d) for improvement in energy ranged from moderate to large. Numerous significant therapeutic effects of TRH administration were observed on several secondary outcome measures monitored in this study. These promising initial findings using i.v. TRH administration in patients with cancer related fatigue are being further explored with orally active TRH formulations.

In terms of practical applications of TRH pharmacotherapy, to date, only a single TRH product has been approved by a regulatory agency and is marketed for clinical use anywhere in the world. The TRH analog Taltirelin, which is marketed under the brand name Ceredist by Mitsubishi-Tanabe Pharma, was approved by the Japanese regulatory agency in 2000 and has been marketed in Japan, since 2000, for the indication of spinocerebellar degeneration (Gary et al., 2003). There is a lack of reports in English language journals detailing the evidence in support of the efficacy of taltirelin in patients with spinocerebellar degeneration. Nevertheless, the safety data reviewed by the Japanese regulatory agency were sufficiently benign to allow approval of taltirelin for this indication, and the compound has been marketed in Japan, since

2000, with a progressive increase in reported sales. The positive reception of this TRH product over the 13-year period of availability in Japan provides some support for the proposal that a TRH product can be used with acceptable safety and tolerability in human subjects. With regard to clinical translational opportunities related to TRH, it is pertinent to note that Kubek et al. (2009) have developed a microsphere nasal spray formulation of TRH and have demonstrated the utility of this formulation in an animal model of seizure induction. Kubek and colleagues have recently received funding from the Department of Defense to examine the utility of this TRH nasal spray formulation in the treatment of suicidality.

In summary, TRH was the first of the hypothalamic releasing hormones to be isolated and characterized, a landmark discovery that revolutionized the field of neuroendocrinology. TRH has been firmly established to play a key role in the CNS regulation of thyroid axis function, and studies of the physiology of TRH have been essential for elucidating mechanisms involved in the regulation of thyroid function. Soon after the discovery of TRH, studies were conducted in both animal models and in patients with depression that suggested that this tripeptide demonstrated behavioral activity and had the potential to bring about rapid improvement in symptoms of depression. While some more recent studies have supported the potential efficacy of TRH in improving symptoms of depression, other studies have failed to demonstrate beneficial effects, and additional work is clearly needed to evaluate the clinical utility of a TRH-based intervention in the treatment of depression. Considerable basic science data supports the proposal that TRH plays a significant role in the CNS, including the possibility that it functions as a CNS neurotransmitter in addition to its classically identified role as a hypothalamic hypophysiotropic agent. The TRH Hypothesis of Homeostatic Regulation suggests that in states of CNS hypoarousal, administration of TRH results in an increase to normal levels of CNS activity, whereas, in states of CNS hyperarousal, administration of TRH serves to modulate the excessive CNS activity towards normal. Numerous therapeutic applications can be identified based on this TRH Hypothesis of Homeostatic Regulation. A few limited examples of translational studies with TRH or TRH analogs were discussed. Clearly, more evidence is needed to confirm and extend data supporting the clinical potential for TRH pharmacotherapy. It must be noted that, to date, only a single TRH compound, the analog taltirelin, has been approved by a regulatory agency and is marketed for clinical use. Thus, the promise of TRH to contribute to the treatment of patients with a broad range of disorders has not yet been realized, but a strong scientific base

of knowledge has been developed to inform further research efforts to validate the therapeutic potential of this approach.

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December 19, 2013

Collated by Olaf Fjetland (September 7, 2017)