Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Thyrotrophin-Releasing Hormone

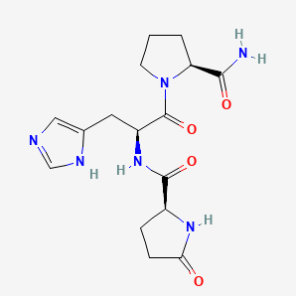
Evidence Summary

TRH may promote consciousness after subarachnoid hemorrhage or head trauma, but cognitive effects in other conditions are mixed. It transiently increases blood pressure, heart rate, and body temperature.

Neuroprotective Benefit: TRH increases arousal but does not consistently affect cognition. TRH may promote consciousness after subarachnoid hemorrhage or head trauma. TRH analogs have shown some neuroprotective benefits in preclinical studies.

Aging and related health concerns: There have not been many studies testing TRH in age-related diseases. One small study suggested that TRH treatment may reduce fatigue in cancer patients.

Safety: TRH transiently increases blood pressure, heart rate, and body temperature. TRH should not be administered to people in whom a marked, sudden change in blood pressure would be dangerous.

Availability: not FDA-approved as a treatment; available as a component of the TRH test as an adjunctive agent in the diagnostic assessment of thyroid function	**Dose**: Dose has not been established for any indication. Several clinical studies have tested intravenous doses of 2 mg.	**Chemical formula:** $C_{16}H_{22}N_6O_4$ **MW**: 362.38  Source: PubChem
Half-life: plasma half-life of 5-7 minutes; peak CSF levels at around 40 minutes; some TRH analogs have longer half-lives	**BBB**: poorly penetrant	
Clinical trials: The largest clinical trial was in 97 patients with subarachnoid hemorrhage who received TRH tartrate.	**Observational studies**: none available	

What is it?

Thyrotropin releasing hormone (TRH) is a tripeptide hormone (pyroglutamyl-histidyl-proline amide) produced by hypothalamic neurons and it stimulates the release of thyroid-stimulating hormone (TSH) and prolactin from the anterior pituitary. Aside from its effects on the thyroid, TRH also exerts neuroprotective actions through effects on cellular bioenergetics, ionic homeostasis, and cerebral blood flow following brain injury (Faden et al., 2005).

TRH is rapidly degraded by the TRH-degrading ectoenzyme, has poor bioavailability, and produces unwanted neuroendocrine, autonomic, and analeptic (CNS-stimulating) side effects; various TRH analogs have been developed to overcome these issues (Scalabrino et al., 2007).

The TRH analog, protirelin tartrate (Hirtonin by Takeda Pharmaceuticals, Japan; and Bognin by Nichiiko Pharmaceuticals, Japan), is currently used in Japan to promote recovery from disturbance of consciousness after aneurysmal subarachnoid hemorrhage and head trauma (Shibata et al., 2019).

Neuroprotective Benefit: TRH increases arousal but does not consistently affect cognition. TRH may promote consciousness after subarachnoid hemorrhage or head trauma. TRH analogs have shown some neuroprotective benefits in preclinical studies.

Types of evidence:

- 6 clinical trials (2 in Alzheimer's patients, 1 in healthy volunteers, 1 in depressed patients receiving electroconvulsive therapy, 1 in cognitively impaired alcoholics, and 1 in patients with subarachnoid hemorrhage)
- Numerous laboratory studies with TRH and TRH analogs

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There have been several clinical studies testing TRH: 2 trials in Alzheimer's patients, 1 in healthy volunteers, 1 in depressed patients receiving electroconvulsive therapy, 1 in cognitively impaired alcoholics, and 1 in patients with aneurysmal subarachnoid hemorrhage. All of these studies have tested acute treatments of TRH, except for the study in subarachnoid hemorrhage.

In a double-blind randomized placebo-controlled trial of 12 healthy older adults (mean age, 64.9 years), treatment with high-dose TRH (0.5 mg/kg, i.v.) did not attenuate scopolamine-induced cognitive impairment, and paradoxically, subjects performed statistically worse receiving TRH after scopolamine, compared to the group given scopolamine alone ($p<0.01$)(Molchan et al., 1992). This high dose was chosen based on the aim to obtain central cognitive effects despite low blood-brain barrier penetration of TRH. No significant correlations were found between behavioral measures of alertness or drowsiness and cognitive scores. When these older adults received TRH alone (0.5 mg/kg, i.v.), without scopolamine, cognitive scores were unchanged or declined from baseline.

These findings were in contrast to a previous study by the same group. In a double-blind randomized placebo-controlled trial of 12 healthy volunteers (mean age, 26.9 years), high-dose TRH infusion (0.5 mg/kg; Peninsula Laboratories; i.v. bolus, 1-minute infusion) markedly attenuated scopolamine-induced impairment of memory function (measured by the selective reminding task) compared to placebo (Molchan et al., 1990). Scopolamine-induced decline in recognition memory (list of new words) and category retrieval (letter portion of the test) were significantly attenuated with TRH treatment. Scopolamine-induced decline in backward digit span was attenuated on the days subjects received TRH. Scopolamine-induced decline in object recall showed a trend for attenuation with TRH. The vigilance-

attention score was unaffected by TRH and was unchanged from baseline after either scopolamine+placebo or scopolamine+TRH. Free recall was also not improved by scopolamine+TRH compared to scopolamine+placebo. Scopolamine-induced decline in automatic processing task was not restored with TRH. It is not clear from this study whether the analeptic effects (CNS-stimulating effects) of TRH played a role in some of the cognitive effects, though no changes in attention or concentration were observed on the vigilance-attention and forward digit span tests.

Subarachnoid hemorrhage due to ruptured cerebral aneurysms has a poor prognosis, with many patients suffering from neurological dysfunction or prolonged issues with consciousness. The TRH analog, protirelin tartrate (Hirtonin by Takeda Pharmaceuticals, Japan and Bognin by Nichiiko Pharmaceuticals, Japan), is currently used in Japan to promote recovery from disturbance of consciousness after aneurysmal subarachnoid hemorrhage and head trauma (Shibata et al., 2019). In a clinical study of over 200 patients with prolonged disturbance of consciousness due to aneurysmal subarachnoid hemorrhage, 97 patients were treated with the TRH-tartrate analog (2 mg/day, i.v.; mean treatment duration of 16.4 days) and their outcomes were compared to 11 patients who did not receive TRH-tartrate treatment (Shibata et al., 2019). There was a statistically significant difference in the change in Hasegawa dementia rating scale-revised (HDS-R) score between the TRH-tartrate-treated group (increased by 10±6.6 points) and the untreated group (increased by 3±2.7 points), with the TRH-tartrate treatment group showing significantly greater improvement (p=0.0003). HDS-R scores were taken 7 days after clipping the aneurysm and 2 days after completing a course of TRH-tartrate treatment. Improvement was especially pronounced in young patients with HDS-R scores between 5 and 20. Poor outcomes were correlated with age greater than 60 and initial HDS-R scores at or lower than 4 points. Because this study was a retrospective study without a placebo group, these findings need to be interpreted with caution. The reasons for why patients did not receive TRH-tartrate varied, including the doctors' judgment that their condition was due to liver dysfunction, fever, and others, so the treated and untreated groups may have been fundamentally different in the pathology of subarachnoid hemorrhage.

In a double-blind placebo-controlled crossover trial of 18 cognitively impaired alcoholics, TRH treatment (0.5 mg, i.v., followed by 2.0 mg i.v. for 10 minutes) did not significantly affect the selective reminding test, the controlled oral word association test, the digit span test, or the Wechsler memory scale (Khan et al., 1993). However, there was a general pattern of marginally better performance after TRH infusion compared with placebo infusion, of minimal effect sizes. When analyses were performed based on duration of drinking, patients with a shorter duration of alcohol use (mean of 16 years) showed significant improvement in verbal learning and memory (total number of words learned on the selective

reminding test) compared to placebo, with a large effect size. Performances on the controlled oral word association test and the digit span test were better with TRH, but did not reach statistical significance; and no difference in performance on the Wechsler memory scale was seen with TRH versus placebo. In patients with a longer duration of alcohol abuse (20+ years; mean of 27 years), there was no improvement in any of the cognitive measures with TRH compared with placebo. The mean duration of abstinence from alcohol was 82.7 days.

In a double-blind placebo-controlled crossover trial of 8 patients with depression who were receiving electroconvulsive therapy (ECT), low-dose TRH (0.5 mg, i.v.) 5 minutes after session 3 or 4 of ECT resulted in a significant difference in the level of consciousness and a small change in some neuropsychological tests, when compared with the placebo infusion (Khan et al., 1994). Fifteen minutes after TRH infusion, 7 out of 8 patients were rousable and 1 was fully awake, while only 4 out of 8 were rousable 15 minutes after placebo infusion. After 30 minutes, 7 out of 8 patients were fully awake after TRH infusion and one was rousable, compared to 7 who were rousable and 1 who was still not responsive to stimuli 30 minutes after placebo infusion. Immediate and delayed verbal memory (measured by Wechsler memory scale and the Buschke selective reminding test) were not significantly different between TRH and placebo conditions. However, TRH infusion was associated with improved performance on verbal initiation and fluency on brief auditory attention span.

Human research to suggest benefits to patients with dementia:

In a double-blind randomized placebo-controlled trial of 10 Alzheimer's patients, treatment with high-dose TRH (0.5 mg/kg, i.v.) showed statistically significant improvement from baseline on the selective reminding task (a measure of new learning and memory), and at a trend level of significance on the estimation of word frequency (measure of automatic processing)(Molchan et al., 1992). When the anticholinergic cognition-impairing drug, scopolamine, was administered prior to TRH, recognition of twice-presented words and backward digit span were significantly better compared to the group receiving scopolamine alone, though no effects of TRH were seen in 9 other cognitive scores. For subjects with the highest Wechsler Memory Scale scores (n=4), and whose dementia severity was mild to moderate, performance improved on more tests (selective reminding test free recall, selective reminding test recall consistency, automatic processing, and free recall of twice-presented words), and to a greater degree.

In a different randomized double-blind clinical trial of 10 Alzheimer's patients, TRH treatment significantly increased arousal, improved affect, and modestly improved semantic memory (measured

by category retrieval; difference of 3.8 + 1.2 words, a 34% difference in change from baseline) (Mellow et al., 1989). On day 1, every patient received TRH (0.1 mg/kg, single-blind), then on days 2 and 3, patients received TRH (0.3 mg/kg, i.v. bolus, 1-minute infusion) or placebo (i.v., 1-minute infusion) in a randomized fashion. TRH treatment (0.3 mg/kg) did not significantly affect attention (measured by the vigilance task), episodic memory (measured by the Buschke task) or visual memory (measured by the picture recognition task). TRH treatment also significantly increased motor activation (compared to baseline), which was likely dopaminergically mediated. The modest improvement in semantic memory could possibly be due to the arousing effects of TRH, though measures of attention were not affected.

In a cerebral spinal fluid (CSF) study of patients with senile dementia (n=19), cerebral tumors (n=49), and disc lesions (n=51), patients with senile dementia had low TRH levels (mean values: 26.5 pg/ml in senile dementia patients; 78.3 pg/ml in disk lesion patients; 69.7 pg/ml in cerebral tumor patients)(Oram et al., 1981).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

TRH has been shown to exert neuroprotective actions through effects on cellular bioenergetics, ionic homeostasis, and cerebral blood flow (Faden et al., 2005).

In rats, TRH treatment (1 and 50 µg, intracerebroventricularly) did not significantly alter performance on the two-choice visual discrimination task, though the treatment increased perseverative responding on one lever (Andrews and Sahgal, 1984).

Because TRH has a short half-life (5-7 minutes) and produces unwanted neuroendocrine, autonomic, and analeptic effects, various TRH analogs have been developed to overcome these issues (Scalabrino et al., 2007).

JAK4D: JAK4D [Glp-Asn-Pro-D-Tyr-D-TrpNH(2)] is a TRH analog that potently inhibits the TRH-degrading ectoenzyme, thereby preventing the degradation of TRH, and binds to central TRH receptors producing actions in the brain without promoting the release of thyroid-stimulating hormone (TSH)(Scalabrino et al., 2007). JAK4D showed high plasma stability, potent inhibition of the TRH-degrading ectoenzyme (K_i=151 nM) with high affinity binding to central TRH receptors (K_i=6.8 nM). In rats, JAK4D administration (1 mg/kg, i.p.) increased activity scores (grooming, chewing, licking, and wet-dog shake), similar to TRH, but with a slower onset of action and to a lesser degree.

In a subsequent study, JAK4D was shown to bind selectively with nanomolar affinity to native TRH receptors in human hippocampal tissue and that these receptors are pharmacologically distinct from TRH receptors expressed in the human pituitary (Kelly et al., 2015). The hippocampal TRH receptor subtype is unclear, but it could be a variant of TRH receptor 1 (TRHR1) or a currently unidentified receptor. *Kelly is the inventor on patents/patent applications relating to JAK4D and is a director and shareholder of NeuroPath Therapeutics Limited, a university spinout company.

In rats subjected to kainate-induced cognitive deficits, JAK4D treatment (10 mg/kg, i.p., 40 minutes before kainate acid) significantly attenuated recall deficits and reduced the formation of hydroxylated derivative of sodium terephthalate (OH-TA), a measure of highly reactive oxygen species (Kelly et al., 2015). Reduction of oxidative stress appears to be one way in which JAK4D may exert neuroprotective effects. An ex vivo study of striatal tissue showed that JAK4D pre-treatment also significantly reduced kainate-induced apoptosis (measured by TUNEL immunolabeling and caspase-3 activation).

In a mouse model of amyotrophic lateral sclerosis (G93A-SOD1 mice), JAK4D treatment (2 mg/kg, i.p., 5 days per week) from 6 months of age consistently and significantly improved rotarod performance and reduced weight loss compared to that of vehicle treatment (Kelly et al., 2015). Rotarod performance in the JAK4D-treated group was enhanced by 21% at first measurement (Day 105) following onset and by 109% on the last day of measurement (Day 114). Median survival for the vehicle-treated group was 126 days (95% CI, 123.4 to 128.6), while it was extended to 132 days (95% CI 130.0–133.1) with JAK4D treatment. JAK4D treatment also showed a statistically significant difference compared to placebo on the mean neuron counts in the ventral horns of the caudal lumbar spinal cord sections.

8c: A synthetic TRH-like peptide, 8c, has shown activity in the central nervous system without altering rat plasma TSH levels (Meena et al., 2015). In a mouse model of cerebral ischemia-induced cognitive impairment (middle cerebral artery occlusion model), treatment with 8c (10 µmol/kg) significantly reduced infarct volume, improved neurological score, improved cognitive functions (measured by the passive avoidance test and the water maze text), reduced oxidative stress markers (lowered MDA levels), and enhanced CA1 neuronal survival. The 8c peptide modulates TRHR2 and has a lower probability of degradation by the TRH-degrading ectoenzyme compared to TRH.

35b, 144, 606, and 807: Several cyclic dipeptides (35b, 144, 606, and 807) structurally related to the TRH metabolite cyclo-His-Pro have been tested *in vitro* and *in vivo* (Faden et al., 2005). In primary neuronal cultures, all 4 peptides (35b, 144, 606, and 807) reduced cell death after physical trauma or trophic withdrawal. Two of these peptides, 35b and 606, also protected against glutamate toxicity and beta-

amyloid-induced injury. In a mouse model of brain injury (subjected to controlled cortical impact), treatment with each of these peptides significantly improved motor and cognitive recovery, while markedly reducing lesion volumes; 35b showed the greatest reduction in lesion volume. Treatment with all 4 peptides showed significantly reduced latencies to find the submerged platform on the Morris water maze. In a rat model of traumatic brain injury (induced by fluid percussion), treatment with 35b (1 mg/kg, via tail vein catheter) after injury significantly down-regulated expression of mRNAs for cell cycle proteins, aquaporins, cathepsins and calpain in ipsilateral cortex and/or hippocampus, while up-regulating expression of the neurotrophic factor BDNF, hypoxia-inducible factor, and several heat-shock proteins.

In other studies from the same group, the 4 peptides were shown to attenuate both apoptotic and necrotic cell death in primary neuronal cultures, significantly reduce intracellular calcium accumulation after injury, and limit changes in mitochondrial membrane potential and associated cytochrome c release (Faden et al., 2004; Faden et al., 2003; Faden et al., 1999). With 35b, dose-response studies showed an inverted U-shaped dose response curve between 0.3 and 3 mg/kg, with a therapeutic window of at least 8 hours. In vitro studies showed that 35b reduced both apoptotic (trophic withdrawal, amyloid-β) and necrotic (maitotoxin, glutamate, oxygen/glucose deprivation) cell death. In apoptotic models, 35b reduced the decline in mitochondrial membrane potential, caspase activation, and the release of cytochrome c and apoptosis-inducing factor (AIF). Unlike TRH, 35b did not induce changes in mean arterial pressure, body temperature, or TSH release, and did not have analeptic activity (Faden et al., 2003). Also, 35b did not show significant binding affinity to TRH receptors or to more than other 50 classical receptors or transporters

In 2007, 35b was under development by RemeGenix Inc. for clinical trials in head injury (Stoica et al., 2009; ScripPharmaIntelligence.Informa.com). However, outcomes of these studies could not be found.

NS3: NS-3 (CG3703; N-[[(3R,6R)-6-methyl-5-oxo-thiomorpholinyl] carbonyl]-L-histidyl-L-prolinamide tetrahydrate) is a TRH analog that has been studied in several models of cognitive impairment (Ogasawara et al., 1995). NS-3 at doses between 0.03-1 mg/kg produced no changes in passive avoidance response in naïve rats, but NS-3 treatment (0.05-0.3 mg/kg) significantly prevented the scopolamine-induced disruption of passive avoidance response. In a model of electroconvulsive shock-induced memory impairment, NS-3 treatment (0.3-1.0 mg/kg, i.p.) significantly improved passive avoidance response. In a model of cycloheximide-induced memory disruption, NS-3 treatment (0.05 mg/kg) significantly reversed deficits in the passive avoidance response, while TRH treatment failed to show an effect at all doses tested (1-30 mg/kg). In a model of hypercapnia-induced learning deficit, NS-

3, treatment (0.1-1.0 mg/kg) significantly reversed the deficit of learning, while TRH at doses of 10-50 mg/kg showed no effect. The authors speculated that the differences in effects between TRH and NS-3 may be due to the differences in biological half-lives in rat plasma.

RX77368: In rats subjected to scopolamine-induced cognitive deficits, pretreatment with a TRH analog, RX77368 (3,3'-dimethyl-TRH; 2 µg, intracerebroventricularly, once daily), produced a partial but significant attenuation of deficits in the 8-arm radial maze (Watson et al., 1994). The authors speculated that RX77368 improved performance by increasing arousal and exploratory behavior in rats rather than directly enhancing cognition.

APOE4 interactions: Unknown

Aging and related health concerns: There have not been many studies testing TRH in age-related diseases. One small study suggested that TRH treatment may reduce fatigue in cancer patients.

Types of evidence:

- 1 randomized controlled trial in patients with cancer-related fatigue

TRH is used as an adjunctive agent in the diagnostic assessment of thyroid function (Drugs.com), but has not been extensively tested for the treatment of age-related diseases.

In a small placebo-controlled randomized crossover trial of 8 patients with cancer-related fatigue, TRH treatment (infusions of 0.5 mg, 0.5 mg, 1.5 g, and 1.5 mg in week 1, 2, 3, and 4, respectively) was associated with significant improvements in fatigue (measured by the VAS-E, the subscale from POMS, and subscale of FACIT-F) and vigor (subscale from POMS), while also showing a trend for improving quality of life (Kamath et al., 2012). The effect sizes (Cohen's d) for one of the fatigue measures (VAS-E) were in the moderate to large range for both TRH doses (1.05 for 0.5 mg TRH and 0.72 for 1.5 mg TRH). Symptoms of sleep disturbance (measured by LSEQ) showed significant improvement with TRH treatment in comparison with placebo, while the walking test scores and anxiety and depression symptoms (measured by HADS) did not show statistically significant difference between TRH and placebo conditions. TRH administration was associated with transient increases in blood pressure and heart rate.

Safety: TRH transiently increases blood pressure, heart rate, and body temperature. TRH should not be administered to people in whom a marked, sudden change in blood pressure would be dangerous.

Types of evidence:

- 7 clinical trials (2 in Alzheimer's patients, 1 in healthy volunteers, 1 in depressed patients receiving electroconvulsive therapy, 1 in cognitively impaired alcoholics, 1 in patients with subarachnoid hemorrhage, and 1 in cancer-related fatigue)
- Numerous laboratory studies with TRH and TRH analogs

In a double-blind randomized placebo-controlled trial of 12 healthy older adults (mean age, 64.9 years) and 10 Alzheimer's patients, treatment with high-dose TRH (0.5 mg/kg, i.v.) after a scopolamine challenge produced a shivering response in all subjects and an unusual taste in 3 patients (Molchan et al., 1992). In Alzheimer's patients, systolic and diastolic blood pressures were higher, along with body temperature after scopolamine + TRH compared to scopolamine alone. In healthy subjects, only the systolic blood pressure was significantly higher with scopolamine + TRH compared to scopolamine alone.

In a double-blind randomized placebo-controlled trial of 12 healthy volunteers (mean age, 26.9 years), high-dose TRH infusion (0.5 mg/kg; Peninsula Laboratories; i.v. bolus, 1-minute infusion) following a scopolamine challenge did not significantly alter blood pressure, heart rate, or body temperature, even though the peak systolic and diastolic blood pressures were significantly higher with TRH (129.5±16.6 mmHg; 87.3±16.5 mmHg) compared to placebo (117.8±11.7 mmHg; 67.9±11.9 mmHg)(Molchan et al., 1990). The mean peak heart rates were not different between scopolamine+placebo and scopolamine+TRH conditions.

In a different randomized double-blind clinical trial of 10 Alzheimer's patients, TRH treatment (0.1 mg/kg on day 1, then 0.3 mg/kg, i.v. bolus, 1-minute infusion on days 2 and 3) was well-tolerated without major adverse reactions (Mellow et al., 1989). Most patients experienced transient shivering, urinary urgency, and hot and cold cutaneous sensations. TRH treatment resulted in significant but transient increase in systolic blood pressure (placebo, 5.1±2.6 mmHg; TRH 0.1 mg/kg, 13.4±4.2 mmHg; TRH 0.3 mg/kg, 23.4±3.9 mmHg). There were no statistically significant effects of TRH infusions on diastolic blood pressure, heart rate, or body temperature.

In a double-blind placebo-controlled crossover trial of 18 cognitively impaired alcoholics, TRH treatment (0.5 mg, i.v., followed by 2.0 mg i.v. for 10 minutes) did not result in untoward reactions, though all

patients exhibited a cardiovascular response (Khan et al., 1993). Both the 0.5 mg and 2.0 mg doses of TRH increased blood pressure and heart rate in most patients, with the peak occurring 2-3 min into the 10-min infusion period. Heart rate was increased by 4-6 bpm and 6-8 bpm with 2.0 mg and 0.5 mg TRH, respectively. Systolic blood pressure was increased by 16-20 mmHg and 18-26 mmHg with 2.0 mg and 0.5 mg TRH, respectively. Diastolic blood pressure was increased by 11-13 mmHg and 14-20 mmHg with 2.0 mg and 0.5 mg TRH, respectively.

In a double-blind placebo-controlled crossover trial of 8 patients with depression who were receiving electroconvulsive therapy (ECT), low-dose TRH (0.5 mg, i.v.) 5 minutes after session 3 or 4 of ECT resulted in an increase in heart rate and blood pressure, though the difference was not statistically different from those after placebo infusion (Khan et al., 1994).

In a small placebo-controlled randomized crossover trial of 8 patients with cancer-related fatigue, TRH treatment (infusions of 0.5 mg, 0.5 mg, 1.5 g, and 1.5 mg in week 1, 2, 3, and 4, respectively) produced modest increases in blood pressure and heart rate, nausea, flushing, and bladder sensation (urge to urinate)(Kamath et al., 2012). The increases in blood pressure and heart rate were transient and not clinically significant. One participant experienced dizziness which resolved with normalization of blood pressure and heart rate. One patient, who had a history of migraine headaches, reported exacerbation of headaches during the first TRH infusion (0.5 mg). The headaches for this patient resolved over the next few hours.

JAK4D: JAK4D is a TRH analog that potently inhibits the TRH-degrading ectoenzyme, thereby preventing the degradation of TRH, and binds to central TRH receptors producing actions in the brain without promoting the release of TSH (Scalabrino et al., 2007). No adverse events were observed after either an acute single dose or daily dosing (for up to 3 months) of JAK4D in rat (up to 5 mg/kg, i.p.) or mouse (in wild type C57 B1/6J mice and G93A-SOD1 mice; up to 2 mg/kg, i.p.)(Kelly et al., 2015). In rats, daily administration of JAK4D (5 mg/kg, i.p.) for 24 days had no effect on food/water intake or liver weight. Toxicological screening showed that JAK4D is not cytotoxic.

35b, 144, 606, and 807: Several cyclic dipeptides (35b, 144, 606, and 807) structurally related to the TRH metabolite cyclo-His-Pro have been tested *in vitro* and *in vivo*, and these compounds showed no significant side effects at doses up to 200 mg/kg (Faden et al., 2004; Faden et al., 2003). In rats subjected to lateral fluid percussion-induced traumatic brain injury, 35b treatment (1 mg/kg, i.v.) did not significantly affect blood pressure, body temperature, TSH activity, or latency to recover the righting reflex (Faden et al., 2003).

Drug interactions: Drug interactions with TRH or its analogs have not been studied extensively. TRH should not be administered to people in whom a marked, sudden change in blood pressure would be dangerous (Drugs.com).

Sources and dosing: TRH or its analogs are not FDA-approved for the treatment of any indication. The TRH analog, protirelin tartrate (Hirtonin by Takeda Pharmaceuticals, Japan; and Bognin by Nichiiko Pharmaceuticals, Japan), is currently used in Japan to promote recovery from disturbance of consciousness after aneurysmal subarachnoid hemorrhage and head trauma (Shibata et al., 2019). Dosage has not been established for any indication. Several clinical studies have tested intravenous doses of 2 mg (Khan et al., 1993; Shibata et al., 2019).

Research underway: There are currently no ongoing clinical trials testing TRH as an intervention. TRH analogs are under development.

Search terms:

Pubmed, Google: Thyrotropin releasing hormone

- + cognitive, + meta-analysis, + clinical trial, + safety, + aging

Websites visited for TRH:

- Clinicaltrials.gov (0)
- NIH RePORTER (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com (0)
- PubChem
- DrugBank.ca

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