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Review Article

Thyrotropin-Releasing Hormone: A Powerful Tripeptide With Diverse Effects in Horses

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ABSTRACT

Thyrotropin-releasing hormone (TRH) was the first trophic "factor" from the hypothalamus to be isolated and identified chemically. It was known to have a stimulatory effect on thyroid-stimulating hormone (TSH) production and secretion by cells within the adenohypothesis, and its structure was revealed to be a modified tripeptide: (pyro)Glu-His-Pro-NH_2. Intravenous or intramuscular injection of TRH to horses results in an immediate rise in plasma TSH concentrations, as would be expected. However, it is now known that TRH has consistent effects on four of the other five cell types in the equine adenohypophysis as well. Administration of TRH to horses stimulates not only plasma TSH concentrations, but also plasma prolactin, adrenocorticotropic hormone, and melanocyte-stimulating hormone concentrations. In contrast, administration of TRH simultaneously or within 1 hour before administration of secretagogues for growth hormone (GH) greatly reduces the GH response to the secretagogues. To date, TRH has not been reported to have positive or inhibitory effects on the release of luteinizing hormone or follicle-stimulating hormone from gonadotropes. Whether the noted effects of TRH on cells other than the thyrotropes are physiologic or pharmacologic is not clear. Regardless, a significant clinical utility has developed for the use of TRH in diagnosing thyroid gland disease as well as pituitary pars intermedia dysfunction in horses.
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1. Introduction

Thyrotropin-releasing hormone (TRH) was the first hypothalamic factor to be isolated and chemically identified as a peptide hormone [1]. Two groups working independently in the United States [2,3] reported in 1969 the structure to be a tripeptide: (pyro)Glu-His-Pro-NH_2. The "pyro" prefix before the glutamic acid designator indicates that the amino end of the peptide forms a cyclic ring with the glutamic acid side chain carboxyl group and hence does not have a chemically active amino group like most peptides. This latter characteristic was the last to be deciphered and likely led to the extended period of time that it took for the scientists to finally match chemical structure of TRH to its biological activity [4–6].

Extensive research has been performed and reported on the biological activity of TRH in various species. The purpose of this review is to concentrate on what is specifically known for the horse regarding TRH activity and how that knowledge has been applied in research and clinical settings in the horse industry. For such a small molecule, TRH has an amazing diversity of effects on hypophyseal hormones in addition to the expected effects on thyroid-stimulating hormone (TSH).

2. TRH and TSH

The first reported use of TRH to stimulate TSH in equine research was by Thompson et al [7] in 1983. Daily

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treatment with 100 μg of TRH was used as a means to potentially stimulate plasma prolactin (PRL) concentrations in seasonally anovulatory mares. Plasma concentrations of TSH were measured around the first injection of TRH (or vehicle; administered intramuscularly) in treated and control mares, and TSH concentrations were found to increase in the first 30 minutes after TRH injection, peak at 1 and 2 hours after injection, and then decrease gradually over the next 2–4 hours. Those authors reported no effect of the TRH treatment on PRL concentrations and no effect overall of daily treatment on reproductive characteristics of the anovulatory mares.

The following year (1984), Thompson and Nett [8] reported on the seasonal responses of both TSH and PRL to increasing doses of TRH in mares. Doses of TRH administered were 0 (controls), .08, .4, 2, and 10 mg per mare. Relative to the controls, doses of .4 mg and higher produced significant increases in plasma TSH concentrations that were not affected by season. No change in plasma PRL concentrations after TRH was observed in that report [8], apparently due to the heterologous assay used to measure PRL (ovine–ovine basis). Thompson et al [9] subsequently showed that PRL did indeed increase in response to TRH under the same circumstances when measured with an equine-canine–based assay.

In a follow-up experiment to that of Thompson et al [7], Gentry et al [10] treated seasonally anovulatory mares with vehicle only, TRH (5 μg/kg of body weight [BW]), a gonadotropin-releasing hormone (GnRH) analog (50 ng/kg BW), or both, daily for 28 days. Plasma concentrations of both TSH and PRL were immediately stimulated by the TRH injections; however, the magnitudes of the responses were greatest on the first day of treatment, decreased by the second day, and were minimal thereafter through day 22. A final assessment of the TSH response to TRH on day 28 indicated a 60% reduction in the TSH response in mares treated daily with TRH relative to control mares. This was the first indication that induced TSH release by TRH injection in horses likely does not immediately stimulate further production of TSH and that repeated daily injections of TRH lead to a depletion of original TSH reserves available for release and an eventual steady state equilibrium of releasable reserves in the long term of about 40%. An alternate explanation could be that repeated TRH injection downregulates TRH receptors, leading to the reduced responses.

The effect of repeated TRH injections in a single day was revealed in a study of the interaction of TRH with the somatotropic axis in horses in which Pruett et al [11] administered geldings 11 hourly injections of either saline (controls) or TRH at 10 μg/kg BW. Plasma TSH concentrations initially increased gradually, peaked between 1.0 and 1.5 hours, and then slowly decreased to pre-TRH concentrations by 8 hours. There was little change in TSH concentrations after the successive TRH injections (i.e., no obvious peaks) after the fourth injection. However, continued elevated concentrations through 8 hours would indicate at least a minimal response to the later injections.

In 2003, Cartmill et al [12] reported the use of TRH to assess the TSH response in mares and geldings that were predetermined to be either normal or hyperleptinemic. Although the leptin status of the horses did not affect the TSH response to TRH, it was found that mares had a greater mean response compared to geldings. Similarly, Arana Valencia et al [13] compared the responses of all adenohypophyseal hormones to separate injections of TRH and sulpiride [13], known secretagogues for hormones associated with pituitary pars intermedia dysfunction (PPID) in horses, in mares that were predetermined to be either insulin sensitive (normal) or insulin insensitive. In that study, mean TSH concentrations, only stimulated by TRH administration but not by sulpiride, were generally higher in mares with normal insulin sensitivity compared to mares that were insulin insensitive.

Other reports involving the measurement of TSH after TRH administration have focused mainly on the hypothalamic-hypophyseal-thyroid axis and perturbations of it. In 2002, Breuhaus [14] used administration of the antithyroidal drug propylthiouracil (PTU) to reduce thyroid activity at the gland itself and subsequently measured plasma concentrations of triiodothyronine (T3) and thyroxine (T4) as well as the TSH response to TRH injection to validate a model of equine hypothyroidism. After 5–6 weeks of PTU feeding, plasma concentrations of TSH increased and the TSH response to TRH was exaggerated, which was consistent with expectations for hypothyroid horses. About the same time, Johnson et al [15] reported that healthy horses fed PTU for 28 days had elevated plasma TSH concentrations, whereas the response to TRH was equivocal. Also in 2003, Pruett et al [11] reported that 52 days of PTU feeding to stallions increased plasma TSH concentrations from a pre-PTU mean of .2 ng/mL to a final concentration of 2.0 ng/mL. The TSH response to TRH was also increased several fold. As opposed to stimulating TSH with PTU feeding, Sommardahl et al [16] used oral administration of levothyroxine sodium to euthyroid horses to inhibit endogenous thyroid hormone release and potentially reduce endogenous TRH and TSH production. Increasing doses of levothyroxine sodium over 8 weeks resulted in the expected reduction in TSH response to TRH.

In an assessment of thyroid function in anhidrotic horses, Breuhaus [17] reported that affected horses had equivalent resting T3, T4, and TSH concentrations to normal horses as well as normal responses of T3 and T4 to TRH injection. Anhidrotic horses differed, however, in their TSH responses to TRH injection, having a greater response overall than normal horses. In a subsequent study of equine neonates, Breuhaus [18] reported that plasma TSH concentrations varied little among normal term foals, normal term but hospitalized foals, and premature foals. Premature foals in general had lower plasma thyroid hormone concentrations as well as a greater TSH response to TRH.

Several other reports in the literature in which thyroid hormones were measured after TRH injection, but TSH concentrations were not, provide limited information on specific topics. Beech and Garcia [19] reported that thyroid hormone responses to TRH injection were similar in normal horses and horses with pituitary adenomas, whereas resting glucose and insulin concentrations were higher. Lothrop and Nolan [20] provided useful information on the timing of T3 and T4 responses to TRH injection, with peak values being observed at 2 and 4 hours after TRH, respectively. Harris et al

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