Exp. Clin. Endocrinol. 99 (1992) 143–146

Experimental and
Clinical Endocrinology

Time-Related Effects of Thyrotropin-Releasing Hormone (TRH) on the Pituitary-Thyroid Axis and Extrathyroidal Targets

M. Nink, P. Weber, U. Krause and J. Beyer

IIIrd Medical Clinic-Endocrinology (Head: Univ.-Prof. Dr. J. Beyer), Mainz University Hospital, Mainz/Germany

Key words: Cardiovascular system – Hormones – Thyrotropin-releasing hormone – Respiration

Summary. Thyrotropin-releasing hormone (TRH) is a tripeptide and acts as a stimulator of the pituitary-thyroid axis as well as having a great number of well defined extrathyroidal functions. Studies in experimental animals have shown, that TRH also has a role as a neuromodulator within the autonomous nervous system.

In this study we analyzed the effects following peripheral administration of TRH (200 μg, 400 μg) in patients with endocrinological disorders and in healthy females and males. By means of a questionnaire, patients were asked about possible (side-) effects; ventilatory and cardiovascular monitoring was performed during steady state. The pulsatile TSH-secretion pattern was analyzed and thyroid and stress hormones were measured in the blood prior to and following TRH i.v.

Frequent symptoms afer TRH were feeling of heat (58%), stimulation of respiration (61%), palpitations (39%), micturition urge (52%) and restlessness (32%). Apparative monitoring demonstrated a short stimulation of respiration and an increase of heart rate. After 400 μg TRH i.v., blood levels of ACTH decreased slightly ($p < 0.01$) but levels of T_3, T_4, epinephrine, norepinephrine and cortisol remained unchanged ($p > 0.05$). TSH-levels were low during daytime and showed a surge at night.

Introduction

Thyrotropin-releasing hormone (TRH) is a phylogenetically ancient neuromodulating tripeptide and classically exerts its effects as a hypothalamic hormone, it also induces a great number of effects beyond the hypothalamo-pituitary pathway (Nemeroff et al., 1979). Results from studies in experimental animals demonstrated a great number of behavioral, neurochemical and electrophysiological effects originating in extrahypothalamic brain areas (Brown, 1989). TRH has been found to be involved in a number of autonomic functions, such as regulation of the cardiovascular and respiratory system by modulation of sympathetic system and vagal tone (Hedner et al., 1983; Iwashita et al., 1990; Siren et al., 1986).

We performed this study in order to investigate the proportions, the dynamics and the time course of autonomous and metabolic effects elicited by TRH after peripheral administration in humans.

Subjects and Methods

Subjects. 277 subjects were comprised in the study: in 220 adult patients of both sexes with various endocrinological disorders, side effects following a 200 μg TRH i.v. injection as a bolus were analyzed by a standardized questionnaire. In a subgroup of normal males cardiac and respiratory function after a 200 μg ($n = 8$) and a 400 μg ($n = 18$) TRH i.v. bolus were monitored. In this latter group we also measured plasma-epinephrine (E), -norepinephrine (NE), -ACTH and cortisol before and 30 minutes after the TRH response. These persons were of normal weight (body-mass index: 22.7 ± 2.4), their age was 18–40 years (27 ± 5 y.).

In addition, in 11 healthy subjects (age: 25 ± 3 y.) we analyzed the dynamics of pituitary TSH release by frequent blood sampling. The relationship of pituitary TSH release and the subsequent T_3 and T_4 secretion of the thyroid were determined in 20 female and male adults who had a normal TSH response prior to and 30 minutes following 200 μg TRH i.v. TRH-application in our subjects was approved by the Mainz Ethics Committee.

Methods. Side effects following the TRH-bolus in all subjects were analyzed by means of a standardized questionnaire

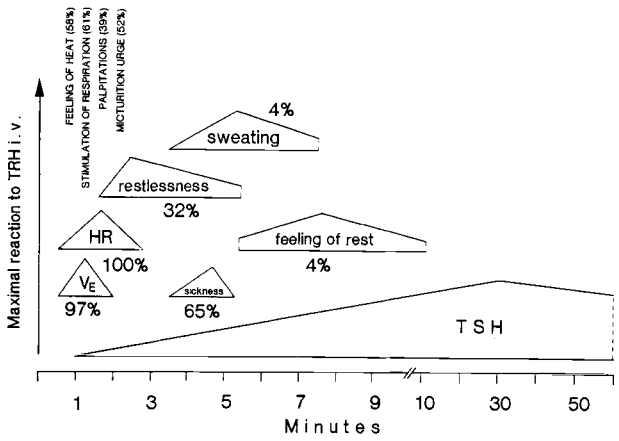

Fig. 1 Prevalence and sequence of (side-) effects in 18 healthy males following 400 µg TRH (30s-bolus i.v. at minute "0"). Symptoms are compared to dynamics of TSH-release as a response to a stimulus of TRH. Prevalence for each symptom is indicated (%) and dynamics of each given effect is symbolized by profile lines. V_E = minute ventilation (l); HR = heart rate (min^{-1})

for quality, frequency and intensity of symptoms, as shown in Fig. 1. Cardiac and spirographic data at rest were determined in 26 male individuals (heart rate, blood pressure, ECG, inspiratory air-flow (V_{in}), end-tidal partial pressure at the mouth of O_2 (pET-O_2) and CO_2 (pET-CO_2)). TRH-injections were placebo-controlled (solvent of TRH), the study design was single blind.

stimulated values. Significance was analyzed by Student's or Wilcoxon's test for paired samples. Mean values and standard deviation (SD) are specified throughout; $p < 0.05$ was considered significant.

Epinephrine and norepinephrine were determined according to methods published by Kringe et al., 1982. TSH was determined by using time resolved immunfluorescence technology (DELFIA®, LKB-Pharmacia, Freiburg), T_3, T_4, cortisol and ACTH were measured radioimmunometrically using standard methods.

Results

Following the TRH-bolus i.v., in all groups our subjects experienced major symptoms, such as feeling of heat, stimulation of respiration, palpitations, micturition urge, restlessness, sweating and feeling of rest (see Fig. 1). After 200 µg TRH and 400 µg TRH side effects were qualitatively similar but we suppose a dose dependent effect. Evaluation of data showed a high interindividual coincidence of symptoms and of their time sequence. Symptoms of a high coincidence are specified in Fig. 1. Starting 25–35 seconds following TRH-injection (200 µg, 400 µg) inspiratory ventilatory air-flow was augmented significantly in our 26 healthy males after both doses of CRH (200 µg, $p < 0.01$; 400 µg, $p < 0.001$, see Tables 1 and 2). Minute volume also increased after both doses of TRH, this increase was only significant after 400 µg TRH i.v. ($p < 0.001$). Heart rate was concomitantly augmented in both groups at an identical time-interval after TRH, these data are specified in Tables 1 and 2; values of plasma-cortisol, -ACTH, -E, -NE, T_3, T_4 and TSH prior to TRH and 30 minutes after TRH are presented in Table 3 in comparison. Blood pressure did not change significantly.

Table 1 Ventilatory parameters and heart rates in 8 healthy young males following 200 µg TRH i.v.

	Placebo	200 µg TRH i.v.	
Inspiratory air-flow:	1.34 ± 0.31 l s^{-1}	1.61 ± 0.29 l s^{-1}	$p < 0.001$
Minute volume:	7.19 ± 1.61 l	8.00 ± 1.98 l	n.s.
Heart rate:	64.9 ± 8.8 min^{-1}	73.5 ± 10.0 min^{-1}	n.s.

n.s. = not significant

Table 2 Ventilatory parameters and heart rates in 18 healthy young males following 400 µg TRH i.v.

	Placebo	400 µg TRH i.v.	
Inspiratory air-flow:	1.35 ± 0.34 l s^{-1}	1.81 ± 0.69 l s^{-1}	$p < 0.001$
Minute volume:	8.23 ± 2.97 l	10.74 ± 4.57 l	$p < 0.001$
Heart rate:	71.8 ± 15.8 min^{-1}	86.1 ± 20.1 min^{-1}	$p < 0.01$

For the evaluation of the spontaneous dynamics of TSH-release frequent blood sampling was performed in 11 subjects via an indwelling venous catheter at intervals of ten minutes over a period of 24 hours. TSH pulse analysis was performed by the DESADE programme (Brabant et al., 1990). The evaluation of the diurnal TSH secretion profiles proceeded from the group mean TSH-level of each interval of blood sampling. For statistical evaluation of our parameters (spirographic data, heart rate and hormones of Table 3) basic values were compared to TRH-

The 24 h pulsatile TSH-secretion in our 11 individuals was quite variable and ranged in females and males from a low to a high TSH-secretion activity, but generally

Table 3 Basal and TRH-stimulated blood-levels of the hormones TSH, T_3, T_4 of 20 healthy subjects and of epinephrine, norepinephrine and ACTH in further 18 healthy individuals. In all persons TSH-response in a TRH-test was physiological

	No.	Prior to TRH	30′ after TRH	
TSH	20	1.5 ± 1.2 μU/ml	8.4 ± 4.7 μU/ml	p = 0.0001*
T_3	20	139 ± 26 ng/100 ml	127 ± 25 ng/100 ml	n.s.*
T_4	20	7.9 ± 1.6 μg/100 ml	7.5 ± 1.5μg/100 ml	n.s.*
Epinephrine	18	25.9 ± 15.5 ng/l	22.0 ± 11.6 ng/l	n.s.$^+$
Norepinephrine	18	29.2 ± 37.3 ng/l	88.4 ± 38.2 ng/l	n.s.$^+$
Cortisol	18	275 ± 109 nmol/l	261 ± 102 nmol/l	n.s.$^+$
ACTH	18	20.6 ± 7.9 pg/ml	17.2 ± 9.0 pg/ml	p = 0.0028$^+$

* = 200 μg TRH i.v., n = 20; $^+$ = 400 μg TRH i.v., n = 18
Statistical evaluation according to Wilcoxon's test for paired samples: n.s. = not significant: $p > 0.05$

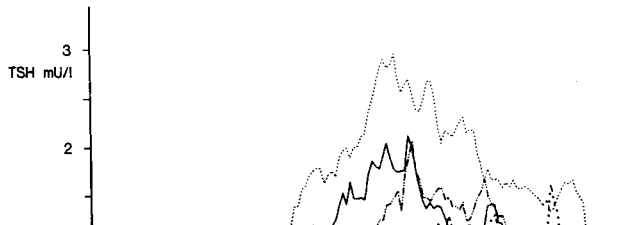

Fig. 2 24-h-pulsatile-TSH-rhythms in four healthy male subjects. Each line shows the spontaneous TSH-secretion-dynamics of one individual

showing a circadian pattern: secretion was low during daytime and exhibited a nocturnal surge, beginning at 11 p.m. (Fig. 2). Mean 24 h serum TSH-level was 0.9 ± 0.4 mU/L, mean TSH-pulses frequency was 9.6 ± 3.5/24 h.

Discussion

Our data indicate, that after intravenous application of standard diagnostic doses of TRH (200 μg, 400 μg) a great variety of effects is provoked within the autonomous nervous system. Symptoms were similar in young healthy subjects and in older patients with various endocrinological disorders. Sex differences were not apparent. Although symptoms in the great majority of our subjects (see Fig. 1) were short lasting and of minor clinical relevance, a few individuals were annoyed by gastrointestinal symptoms (e.g. sickness), palpitations and restlessness. Serious reactions were not observed in our subjects but some severe side-effects have been reported in literature following TRH i.v. (e.g. Meada and Tanimoto, 1981; Dolva et al., 1983; Grussendorf et al., 1982).

Furthermore, evaluation of our data showed a very distinct time sequence of symptoms, starting with cardiovascular effects (e.g. palpitations) and stimulation of respiration during the first minutes after TRH; these initial symptoms were succeeded by gastrointestinal symptoms over several minutes. Peaking of the main effects within the pathways of the autonomous nervous system shows a clear mismatch to the maximal reaction within the pituitary-thyroid axis (i.e. maximal TSH-release after 30 minutes). Thus activation of this endocrine axis may not be responsible for most of our effects observed. Mode of action by systemic TRH on the autonomous nervous system is still speculative: our effects observed may be mediated via fast post-receptor axonal conductance or via the circumventricular organs of the brain (e.g. Pardridge, 1988). In addition, secondary effects (e.g. ventilatory depression following baroreceptor activation) may overlay primary effects (e.g. ventilatory stimulation) and thus may alter net response to TRH. A minor decrease of plasma-ACTH following TRH-application may indicate a direct influence of TRH on the hypothalamo-pituitary-adrenal axis although a bias by the study design cannot be excluded.

In our subjects an average of 9.6 TSH-pulses per 24 h were secreted by the pituitary gland showing a nocturnal surge. This finding is in good accordance with the results of methodologically comparable studies (Brabant et al., 1986, Greenspan et al., 1986). Mechanisms which regulate TSH secretion rhythms are still not completely understood. Clinical studies in humans and cell culture studies suggest that the hypothalamus plays the dominant role in regulating TSH-secretion (Ridgway et al., 1987). Furthermore, pulsatile TSH-secretion is also specifically influenced by water and food restriction (Armario et al., 1987, Romijn et al., 1990). For clinical practice the question arises if the pituitary secretion system and the circadian variation of TSH concentration interfere with hormonal response when performing a TRH-test. When performing a TRH-test in the morning – as it is common clinical practice – TSH values at that time of day accurately reflect the status of the pituitary-thyroid axis throughout the day.

References

[1] Armario, A.; Montero, J. L.; Jolin, T.: Chronic food restriction and the circadian rhythms of pituitary-adrenal hormones, growth hormone and thyroid stimulating hormone. Ann. Nutr. Metab. 31 (1987) 81–87

[2] Bartalena, L.; Martino, E.; Falcone, M.; Buratti, L.; Grasso, L.; Mammoli, C.; Pacchiarotti, A.; Aghini-Lombardi, F.; Balzano, S.; Pinchera, A.: Evaluation of the nocturnal serum thyrotropin (TSH) surge, as assessed by TSH ultrasensitive assay, in patients receiving long term L-thyroxine suppression therapy and in patients with various thyroid disorders. J. Clin. Endocrinol. Metab. 65 (1987) 1265–1271

[3] Brabant, G.; Ranft, U.; Ocran, K.; Hesch, R. D.; vz Mühlen, A.: Thyrotropin – an episodically secreted hormone. Acta Endocrinol. (Copenh.) 112 (1986) 315–322

[4] Brabant, G.; Prank, K.; Ranft, U.; Schuermeyer, T.; Wagner, T. O. F.; Hauser, H.; Kummer, B.; Feistner, H.; Hesch, R. D.; vz Mühlen, A. V.: Physiological regulation of circadiane and pulsatile thyrotropin secretion in normal man and woman. J. Clin. Endocrinol. Metabol. 70 (1990) 403–409

[5] Brown, M. R.: Thyrotropin releasing factor: a putative CNS regulator of the autonomic nervous system. Life Sci. 28 (1981) 1789–1795

[6] Brown, M. R.: (1989) Neuropeptide regulation of the autonomic nervous system. In: Neuropeptides and Stress. Eds. Tache, Y.; Morley, J. E.; Brown, M. R., New York: Springer Verlag 1989, pp. 107–120

[7] Greenspan, S. L.; Klibanski, A.; Schoenfeld, D.; Ridgway, E. C.: Pulsatile secretion of thyrotropin in man. J. Clin. Endocrinol. Metab. 63 (1986) 661–668

[8] Hedner, J.; Hedner, T.; Wessberg, P.; Lundberg, D.; Jonason, J.: Effects of TRH and TRH analogues on the central regulation of breathing in the rat. Acta Physiol. Scand. 117 (1983) 427–437

[9] Iwashita, A.; Kobayashi, I.; Inukai, T.; Takahashi, M.; Ishii, A.; Ohshima, K.; Mori, M.; Shimomura, Y.; Kobayashi, S.: Influence of thyrotropin-releasing hormone on autonomic nervous system determined by the variations in R-R interval on electrocardiogram. Exp. Clin. Endocrinol. 96 (1990) 121–124

[10] Kringe, K. P.; Neidhart, B.; Lippmann, C. H.: Practical aspects of the routine determination by HPLC of free noradrenaline and adrenaline in urine and plasma. In: Practical Aspects of Modern HPLC. Ed. Molnar, I., New York: De Gruyter 1982, pp. 241–273

[11] Nemeroff, C. H. B.; Loosen, P. T.; Bissette, G.; Manberg, P. J.; Wilson, J. C.; Lipton, A.; Prange, A. J. jr.: (1979) Pharmaco-behavioral effects of hypothalamic peptides in animals and man: focus on thyrotropin-releasing hormone and neurotensin. Psychoneuroendocrinology 3 (1979) 279–310

[12] Pardridge, W. M.: Recent advances in blood-brain barrier transport. Ann. Rev. Pharmacol. Toxicol. 28 (1988) 25–39

[13] Ridgway, E. L.; Greenspan, S.; Shupnik, M.: Hypothalamic regulation of thyrotropin biosynthesis and secretion. Horm. Metab. Res. Suppl. 17 (1987) 78–82

[14] Romijn, J. A.; Adriaanse, G.; Brabant, G.; Prank, K.; Endert, E.; Wiersinga, W. M.: Pulsatile secretion of thyrotropin during fasting: A decrease of thyrotropin pulse amplitude. J. Clin. Endocrinol. Metab. 70 (1990) 1631–1636

[15] Siren, A. L.; Feuerstein, G.; Labroo, V. M.; Cohen, L. A.; Lozovsky, D.: Effects of thyrotropin-releasing hormone and some of its histidine analogs on the cardiovascular system and prolactine release in the conscious rat. Neuropeptides 8 (1986) 63–70

Accepted: 3 February 1992

Author's address: Dr. Manfred Nink, IIIrd Medical Clinic – Endocrinology, Mainz University Hospital, Langenbeckstr. 1, W - 6500 Mainz, FRG