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Short Communication

Effects of acute psychosocial stress on the hypothalamic-pituitary-thyroid (HPT) axis in healthy women

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ABSTRACT

Objective: The individual set point of the hypothalamic-pituitary-thyroid (HPT) axis is largely genetically determined. Apart from this genetic predisposition, the HPT axis may also be malleable to environmental demands such as psychosocial stress. Indeed, previous research has indicated that critical life events often precede the onset of autoimmune thyroid diseases, and subtle abnormalities in HPT functioning are present in some patients with stress-related disorders such as depression. However, no studies have investigated whether exposure to psychosocial stress leads to an immediate activation of the HPT axis.

Methods: A total of N = 30 healthy women attended two laboratory appointments in a randomized order. An intravenous catheter was inserted at the beginning of each appointment. In the stress session, this was followed by the Trier Social Stress Test (TSST). Plasma samples to determine thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) were taken at baseline and 20, 50, and 110 min after the TSST started. In the control session, participants rested and were instructed to read magazines, while the sampling schedule was maintained.

Results: There was a significant rise in TSH concentrations in response to the TSST, with a peak observed 20 min after stressor onset, and a steady decline thereafter. No such response was observed in the control session. The TSST did not increase T3 or T4.

Conclusion: The finding that acute psychosocial stress is able to elicit a significant increase in TSH is relevant to our understanding of a number of stress-related illnesses presenting with abnormalities of the HPT axis.

1. Introduction

The major function of the hypothalamic-pituitary-thyroid (HPT) axis is to provide the body with energy by increasing cardiovascular activity, glucose and fat metabolism, gastrointestinal motility, and sweat gland activity. The individual set point of the HPT axis is genetically determined, with heritability estimates lying from 26% to 65% (Medici et al., 2015). Apart from this genetic predisposition, the HPT axis is malleable to environmental demands such as stress.

In rats, acute immobilization has been found to lead to an increase in thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) within two minutes (*e.g.*, Langer et al., 1983) to 30 min (Armario et al., 1987) of stressor onset, with decreased levels two hours later (Langer et al., 1983). In line with these findings, diminished T3 was found two hours after acute electric shocks in male rats (Helmreich et al., 2006). By contrast, another study, which also employed electric shocks, reported elevated T3 concentrations three hours after exposure (Friedman et al., 1999). In healthy men, parachute jumps led to significant increases in TSH within five to 15 min (Schedlowski et al., 1992). In another study in healthy men, TSH levels measured after combined one-hour mental and physical stress in the laboratory did not differ from baseline levels (MacLean et al., 1997). In female medical students, attenuated TSH, but not T3 or T4, was observed after an up to three-hour written academic test (Johansson et al., 1987). Taken together, these studies indicate that the HPT axis is activated in response to a wide range of stressors, although the time trajectories of each

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hormone remain unclear.

Stress research indicates that *psychosocial* stress, which occurs in an interpersonal context, is of particular relevance due to its ubiquity in modern societies and the fact that it is involved in numerous health conditions (*e.g.*, Hammen, 2005). To date, only one study has examined the effects of acute psychosocial stress on the HPT axis, reporting significantly lowered TSH in physicians two hours after delivering a conference lecture, while no changes in T3 or T4 emerged (Pinna et al., 1998). This finding of significant changes in TSH in the aftermath of the lecture resonates well with previous research showing that psychosocial stress may be involved in the development of disorders that present with HPT axis abnormalities. For instance, in autoimmune thyroid diseases, a relationship between critical life events (*e.g.*, divorce) and disease onset has repeatedly been reported (Bagnasco et al., 2006). In addition, a substantial body of research has documented subtle abnormalities in HPT functioning in patients with stress-related mental disorders such as depression and anxiety disorders (Fischer and Ehlert, 2018; Fountoulakis et al., 2006). However, whether the HPT axis is *immediately* activated in response to psychosocial stress remains unknown.

The aim of the present study was thus to investigate for the first time whether TSH, T3 and T4 respond to a validated laboratory paradigm inducing psychosocial stress, using repeated measures of each hormone. Women rather than men were investigated, since they are more frequently affected by stress-related illnesses, and to limit any confounding influence of gonadal hormones on HPT parameters. Based on the above-reported literature in humans, it was hypothesized that TSH would rise within minutes of psychosocial stressor onset, with steady declines thereafter, whereas no increases in T3 or T4 were expected.

2. Methods

2.1. Participants

An a priori power analysis based on prior research in humans (see above) indicated a necessary sample size of N = 24 individuals to detect a medium-sized effect ($\alpha = 0.05$, power of 0.80). A total of N = 30 healthy women from the general population were recruited through newspaper advertisements and flyers. Participants had to be aged 18 or older and fluent German speakers. In addition, they had to be free of physical and mental illnesses, which was confirmed by routine blood testing and the Structured Clinical Interview for DSM-IV during a screening appointment at our laboratory.

2.2. Protocol

All included women attended two laboratory appointments in a randomized order, which took place within approximately one week: a stress session and a control session. All free-cycling women were tested during the luteal phase of the menstrual cycle (confirmed by ovulation testing). Both appointments began at 11.30a.m. After providing written informed consent, an intravenous catheter was inserted into the antecubital vein and participants were instructed to rest and read magazines until 1pm. In the stress session, this was followed by the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), which is the most frequently employed laboratory paradigm to induce psychosocial stress. In brief, the TSST comprises a 5-min mock job interview and a 5-min mental arithmetic task, which are performed in front of a video camera and a committee of experts wearing white lab coats. Psychological stress was measured at baseline (at the end of the resting period), as well as immediately before and after the TSST by means of a visual analogue scale (VAS) ranging from 0-100. Parameters of the HPT axis were measured at baseline and 20, 50, and 110 min after the TSST began. The same measures and time points were used in the control session, in which participants were instructed to continue to read magazines. Participants remained seated throughout both appointments. All procedures were in accordance with the Declaration of Helsinki and the study was approved by the local ethics committee (University of Marburg).

2.3. Biochemical analyses

Plasma samples were immediately stored at −80 °C until biochemical analysis. Enzyme-linked immunoassays (IBL, Hamburg, Germany) were used to determine TSH, T3, and T4. The TSH assay has a detection range between 0.06 and 15 mU/L, the T3 assay has a detection range between 0.1 and 10 ng/mL, and the T4 assay has a detection range between 8 and 250 nmol/L. The intra-assay variation is 3.2–3.9% for TSH, 3.6–6.6% for T3, and 2.5–5.6% for T4. The inter-assay variation is 3.3–9.2% for TSH, 5.2–6.7% for T3, and 4.9–8.1% for T4.

2.4. Statistical analyses

All hormonal data were checked for outliers (3 SD) and normal distribution. Eight outliers were detected in total (one person had a slightly elevated TSH baseline value in the control condition and another person had slightly elevated T3 at almost every time point, both in the control and TSST condition); however, as these were still in a physiologically plausible range and not indicative of hypo- or hyperthyroidism (and as exclusion of these outliers did not change any of the below findings) no cases were removed from the final analysis. While T4 was normally distributed, log-transformation was applied to both TSH and T3 values before statistical analysis. Pearson correlations and independent t-tests were performed to identify confounders of HPT parameters. Repeated measures ANOVAs were performed to test whether there were significant changes in psychological stress (VAS), TSH, T3, and T4 over the course of time (time effect) and between sessions (session effect). A Greenhouse-Geisser correction was used in case of a violation of the sphericity assumption. In the case of significant effects, this was followed by contrasts to pinpoint their origin. The alpha error was set at 5% and all analyses were conducted with SPSS.

3. Results

3.1. Sample characteristics

The mean age of the sample was 37 ± 13 years, with 50% free-cycling women, 33% women on oral contraceptives, and 17% postmenopausal women. The average BMI was 22 ± 3 kg/m^2 and 20% of the sample were smokers. There were no significant correlations between age, BMI and baseline HPT parameters (all $p > .117$). Likewise, there were no significant differences in these measures between free-cycling women, women on oral contraceptives, and postmenopausal women (all $p > .107$), or between non-smokers and smokers (all $p > .463$).

3.2. Effects of psychosocial stress

In terms of psychological stress, significant main effects of time ($F(2, 50) = 12.07$, $p < .001$, partial eta$^2 = 0.336$) and session ($F(1, 25) = 35.35$, $p < .001$, partial eta$^2 = 0.586$) were observed, alongside a significant time by session effect ($F(2, 50) = 12.60$, $p < .001$, partial eta$^2 = 0.335$). Contrasts indicated that these effects were due to a significant increase in psychological stress from baseline to immediately before the beginning of the TSST, which was absent in the control session (time by session effect: $F(1, 25) = 21.97$, $p < .001$, partial eta$^2 = 0.468$).

A similar picture emerged in terms of TSH: Significant time ($F(3, 75) = 8.68$, $p < .001$, partial eta$^2 = 0.258$) and session effects ($F(1, 25) = 361.77$, $p < .001$, partial eta$^2 = 0.935$) were found in addition to a significant time by session effect ($F(3, 75) = 4.14$, $p = .009$, partial

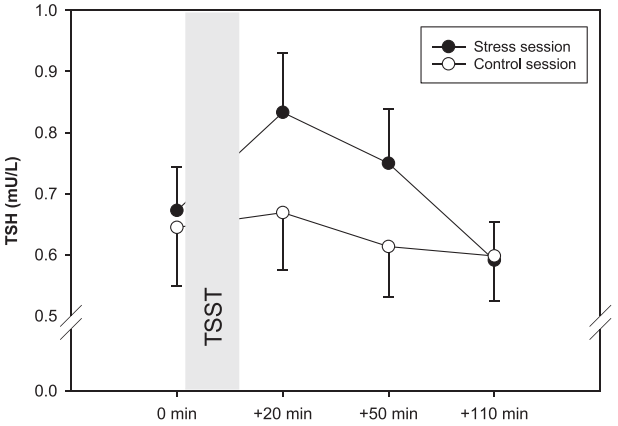

Fig. 1. Thyroid-stimulating hormone (TSH) in the control session (reading magazines) and in the stress session (Trier Social Stress Test; TSST); bars refer to standard errors of mean.

eta^2 = 0.142). Contrasts revealed that these effects were driven by a significant surge of 36% in TSH concentrations within 20 min of TSST onset, and a significant decline between 50 min and 110 min later, which, again, were not found in the control session (time by session effect surge: F(1, 25) = 5.46, p = .028, partial eta^2 = 0.179; time by session effect decline: F(1, 25) = 8.44, p = .008, partial eta^2 = 0.252; see Fig. 1).

By contrast, in terms of T3 and T4, there was neither a significant effect of time (T3: F(1.79, 44.65) = 2.79, p = .078; T4: F(3, 75) = 1.25, p = .297) nor of session (T3: F(1, 25) < 0.01, p = .993; T4: F(1, 25) = 0.64, p = .430). However, both time by session effects were significant, indicating crossover interactions (T3: F(3, 75) = 3.56, p = .018, partial eta^2 = 0.125; T4: F(3, 75) = 3.33, p = .024, partial eta^2 = 0.118). According to contrasts, these were attributable to increases in T3 (time by session effect: F(1, 25) = 8.14, p = .009, partial eta^2 = 0.246) and decreases in T4 (time by session effect: F(1, 25) = 12.83, p = .001, partial eta^2 = 0.246) between the first two measurement time points in the control session, and Fig. 2 suggests that this was mainly a result of attenuated baseline T3 and elevated baseline T4.

4. Discussion

This study yielded two main findings. First, TSH increased within 20 min of psychosocial stress, started to decline at 50 min, and had returned to baseline levels at 110 min, and this pattern was absent in the control session. Second, neither T3 nor T4 increased in response to psychosocial stress.

The first result is in line with an earlier study which revealed significant increases in TSH in parachutists within five to 15 min of a jump (Schedlowski et al., 1992). The present study complements this finding by showing that psychosocial stress is equally capable of triggering short-term TSH responses. Notably, while the rise in TSH was comparable to previous research, the absolute values of our study were lower, which is most likely attributable to different methodologies (*e.g.*, assay, storage conditions) and to the fact that testing took place in the afternoon, when HPT activity is at its nadir (Philippe and Dibner, 2015).

The second result resonates well with an earlier study showing no significant changes in T3 or T4 two hours after giving a lecture (Pinna et al., 1998). The present study extends this finding by demonstrating that thyroid hormones do not appear to increase significantly within 20–50 minutes of psychosocial stress onset. Nevertheless, it is possible that more severe forms of stress occurring in an interpersonal context (*e.g.*, trauma) would evoke significant T3 and T4 responses in humans. Notably, in the present study, the baseline T3 levels in the control condition were markedly attenuated and T4 was slightly elevated. This might be explained by differences in metabolic status (*e.g.*, food intake) prior to the sessions.

Our findings suggest that psychosocial stress is capable of activating parts of the HPT axis. This is important, as critical life events have been shown to precede the onset of autoimmune diseases (Bagnasco et al., 2006) and other disorders that are linked with subtle HPT abnormalities, such as depression (Hammen, 2005). However, the extent to which stress-related fluctuations in TSH exert physiologically meaningful changes in the body remains unknown, especially as T3 and T4 were not affected by the TSST in the present study. This is in contrast to cortisol, the peripheral end product of the hypothalamic-pituitary-adrenal (HPA) axis, which is found to be increased in most subjects facing the TSST (Kirschbaum et al., 1993). However, the HPA analogue of TSH at the pituitary level, adrenocorticotropic-releasing hormone, rises by approximately 200% in response to the TSST, whereas TSH only increased by 36% in the present study. Greater changes in TSH (as, for instance, occurring in response to pharmacological stimulation with thyrotropin-releasing hormone; Frohlich and Wahl, 2019) may thus be necessary to cause significant changes in T3 or T4.

Strengths of this study include the use of a standardized paradigm to induce psychosocial stress, the use of a control session, the use of a

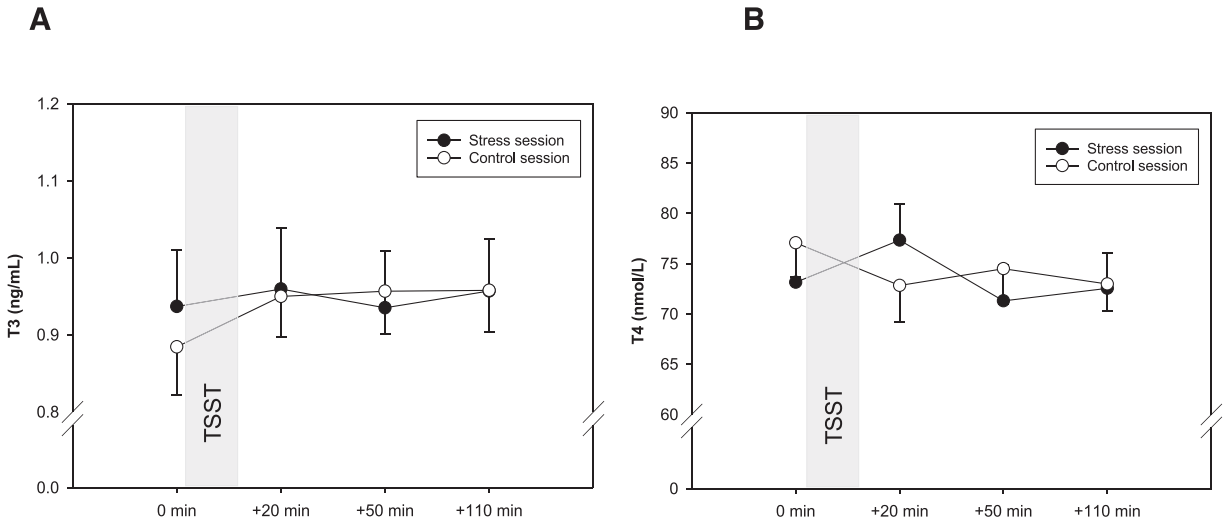

Fig. 2. Triiodothyronine (T3) and thyroxine (T4) in the control session (reading magazines) and in the stress session (Trier Social Stress Test; TSST); bars refer to standard errors of mean.

catheter rather than repeated venipuncture, which may cause stress in itself, and the use of repeated HPT axis measures. Its main limitation is the fact that only women were examined due to a potential confounding impact of gonadal steroids on HPT measures. Nevertheless, it is important to gather data on HPT responses to stress in women, since earlier studies in this area were mostly confined to men. Another limitation is that hormonal analyses were not conducted in duplicates. Notably, while duplicates are always preferable to single determinations, the intra-assay coefficients of variation of the present assays were relatively low (< 7%).

In sum, the present study provides initial evidence that TSH levels increase in response to psychosocial stress, which may prove relevant for our understanding of a number of stress-related illnesses presenting with HPT abnormalities. Future research should investigate the effects of more severe stress on HPT functioning, and examine whether and how fluctuations in the HPT axis may translate into symptoms that are shared by thyroid-related illnesses (*e.g.*, fatigue).

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Declaration of Competing Interest

None.

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References

Armario, A., Garcia-Marquez, C., Jolin, T., 1987. The effects of chronic intermittent stress on basal and acute stress levels of TSH and GH, and their response to hypothalamic regulatory factors in the rat. Psychoneuroendocrinology 12, 399–406.
Bagnasco, M., Bossert, I., Pesce, G., 2006. Stress and autoimmune thyroid diseases. Neuroimmunomodulation 13, 309–317.
Fischer, S., Ehlert, U., 2018. Hypothalamic-pituitary-thyroid (HPT) axis functioning in anxiety disorders. A systematic review. Depr. Anx. 35, 98–110.
Fountoulakis, K.N., Kantartzis, S., Siamouli, M., Panagiotidis, P., Kaprinis, S., Iacovides, A., Kaprinis, G., 2006. Peripheral thyroid dysfunction in depression. World J. Biol. Psychiatry 7, 131–137.
Friedman, Y., Bacchus, R., Raymond, R., Joffe, R.T., Nobrega, J.N., 1999. Acute stress increases thyroid hormone levels in rat brain. Biol. Psychiatry 45, 234–237.
Frohlich, E., Wahl, R., 2019. The forgotten effects of thyrotropin-releasing hormone: metabolic functions and medical applications. Front. Neuroendocrinol. 52, 29–43.
Hammen, C., 2005. Stress and depression. Annu. Rev. Clin. Psychol. 1, 293–319.
Helmreich, D.L., Crouch, M., Dorr, N.P., Parfitt, D.B., 2006. Peripheral triiodothyronine (T(3)) levels during escapable and inescapable footshock. Physiol. Behav. 87, 114–119.
Johansson, G., Laakso, M.L., Karonen, S.L., Peder, M., 1987. Examination stress affects plasma levels of TSH and thyroid hormones differently in females and males. Psychosom. Med. 49, 390–396.
Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The' Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28, 76–81.
Langer, P., Vigas, M., Kvetnansky, R., Foldes, O., Culman, J., 1983. Immediate increase of thyroid hormone release during acute stress in rats: effect of biogenic amines rather than that of TSH? Acta Endocrinol. (Copenh.) 104, 443–449.
MacLean, C.R., Walton, K.G., Wenneberg, S.R., Levitsky, D.K., Mandarino, J.P., Waziri, R., Hillis, S.L., Schneider, R.H., 1997. Effects of the Transcendental Meditation program on adaptive mechanisms: changes in hormone levels and responses to stress after 4 months of practice. Psychoneuroendocrinology 22, 277–295.
Medici, M., Visser, W.E., Visser, T.J., Peeters, R.P., 2015. Genetic determination of the hypothalamic-pituitary-thyroid axis: where do we stand? Endocr. Rev. 36, 214–244.
Philippe, J., Dibner, C., 2015. Thyroid circadian timing: roles in physiology and thyroid malignancies. J. Biol. Rhythms 30, 76–83.
Pinna, G., Hiedra, L., Meinhold, H., Eravci, M., Prengel, H., Brodel, O., Graf, K.J., Stoltenburg-Didinger, G., Bauer, M., Baumgartner, A., 1998. 3,3′-Diiodothyronine concentrations in the sera of patients with nonthyroidal illnesses and brain tumors and of healthy subjects during acute stress. J. Clin. Endocrinol. Metab. 83, 3071–3077.
Schedlowski, M., Wiechert, D., Wagner, T.O., Tewes, U., 1992. Acute psychological stress increases plasma levels of cortisol, prolactin and TSH. Life Sci. 50, 1201–1205.