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Increased Urinary Excretion of Triiodothyronine (T_3) and Thyroxine (T_4) and Decreased Serum Thyreotropic Hormone (TSH) Induced by Motion Sickness

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HABERMANN, J., T. EVERSMANN, F. ERHARDT, M. GOTTSMANN, G. ULBRECHT, and P. C. SCRIBA. *Increased urinary excretion of triiodothyronine (T_3) and thyroxine (T_4) and decreased serum thyreotropic hormone (TSH) induced by motion sickness.* Aviat. Space Environ. Med. 49(1):58-61, 1978.

We exposed 35 male subjects to a rotary chair and motion sickness was provoked by Coriolis effect. This stress caused an increased excretion of urinary T_3 and T_4 and a decrease of TSH levels in serum. The increment in urinary excretion of thyroid hormones may serve as a very useful measure for the quantitation of physical stress. Although no statistically significant change of T_3, T_4, and TBG levels in serum could be observed by the employed techniques, the hypothesis is favoured that motion sickness probably causes an immeasurably small increase of the free thyroid hormone fraction in serum, thereby increasing urinary excretion of T_3 and T_4 and, in turn, decreasing TSH secretion. Physical or psychological stress situations involve most of the endocrine systems. Contradictory results have been reported in the literature concerning the relationship between thyroid function and stress.

MORE THAN 99% of the plasma thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4) are protein-bound; however, only the free hormone can enter the cell and act directly on its metabolism. With normal renal function only the unbound, free thyroid hormone fraction is filtered by the glomerulus. The thyroid hormone excretion in urine may, therefore, parallel the free hormone level in serum (12).

The aim of this study was to investigate the effect of stress on the free thyroid hormone fraction in plasma, by measuring alterations in glomerular filtration and suppression of TSH secretion. The analysis of thyroid hormone excretion in urine offers the additional advantage of an integrated parameter covering a time period in which blood samples are unavailable.

Pilots and aircraft crew are especially exposed to changing acceleration and psychological stress situations. We were, therefore, interested in the response of the pituitary-thyroid axis to experimental stress situations like that of motion sickness.

Hence, the thyroid hormone and TSH levels in serum, as well as the urinary excretion of T_3 and T_4, were measured in soldiers in which motion sickness had been experimentally provoked by the Coriolis effect.

MATERIALS AND METHODS

Fasting male volunteers (N = 35) were exposed from 9 a.m. to increased angular velocity stepwise up to a maximum of 210°/s on a Stille rotary chair. At each step, 20 head movements were executed in the four cardinal directions. Rotation was stopped when frank motion sickness (fms) became obvious by retching or vomiting (4). Hormone analyses were performed on blood samples taken 30 min and immediately before starting rotation, immediately after cessation, and then at 15, 30, 45, 60, 90 and 120 min thereafter. Urinary thyroid hormone excretion was determined in urine obtained from four collecting periods: 6 p.m.-6 a.m. before the rotation experiment, 6 a.m.-12 noon, including the test period, and in the two periods, 12 noon-6 p.m. and 6 p.m.-6 a.m. after rotation.

The determination of urinary excretion of T_3 and T_4 was carried out using sephadex columns with which the extraction, incubation with specific antibodies, and the separation of antibody-bound and free hormones was performed (6). The determination of the catecholamines in urine was performed by the fluorimetric method of Weil-Malherbe (13).

Triiodothyronine (T_3) and thyroxine-binding-globulin (TBG) in serum were measured by radioimmunoas-

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say (7,8) and thyroxine (T_4) was determined with a competitive protein binding assay (7). The T_3-uptake (T_3U) was performed on small sephadex columns (7).

In order to increase the assay sensitivity, the radioimmunological determination (3) of thyroid stimulating hormone (TSH) was slightly modified. By prolonging incubation time and by doubling the amount of serum in the sample the sensitivity of the assay was trebled.

RESULTS

Normal values: The normal range of thyroid hormone excretion in urine was measured from 20 healthy, normal persons. The excretion of T_3 was 1.70 ± 0.40 μg and of T_4 1.44 ± 0.51 μg (mean ± S.D.) per 24 h.

The urine of 11 pilots was collected during daytime over 3-h intervals (6 a.m.-9 a.m., 9 a.m.-12 noon, 12 noon-3 p.m., 3 p.m.-6 p.m., 6 p.m.-9 p.m.) and during the night in one 9-h interval (9 p.m.-6 a.m.). The persons under test were awakened at 6 a.m. and submitted to a psychological test during the day. The mean thyroxine excretions after 9 a.m. were approximately 70% higher than the excretion during the night and remained constant during the day. The excretion of T_4 from 6 a.m.-9 a.m. did not differ significantly from that during the night. A comparable diurnal rhythm for T_3 was not observed.

The normal range of catecholamine excretion in urine was measured from 10 healthy normal persons. An excretion of 5.77 ± 1.76 μg epinephrine and of 15.25 ± 5.38 μg norepinephrine (mean ± S.D.) per 24 h was observed.

The epinephrine excretion showed a clear diurnal rhythm. The excretion during the day was 115% higher compared with that during the night. In contrast, norepinephrine showed only a 38% higher excretion during the day than during the night.

Rotation experiment: The urinary excretion of thyroid hormones was determined in four pilots taken off duty because of susceptibility to motion sickness, four qualified pilots, and 23 normal volunteers. Four of the volunteers were retested under the same stimulus for reproducibility and two were tested on the rotary chair without the head movements as a control. Taken together, all the candidates excreted 1.51 ± 0.67 μg T_3 (mean ±S.D.) and 0.97 ± 0.60 μg T_4 during 24 h. These values were lower than those of the normal group, but did not differ from the values found in patients with endemic goitre (6). Therefore, one may assume that a considerable number of the persons tested had endemic goitre, which is plausible because of the high frequency of this disorder in the south of the German Federal Republic (9).

In order to compensate for the individual differences in thyroid hormone excretion, the percentage increase above 100% in hormone excretion was individually calculated taking the night period after the rotation test as the 100% reference. It was shown (Fig. 1) that the thyroid hormone excretion was already higher before the test (T_3:61 ± 23%, T_4:91 ± 25% above control, mean ± S.E.) and that it increased significantly during the tests in comparison with the normal diurnal rhythm

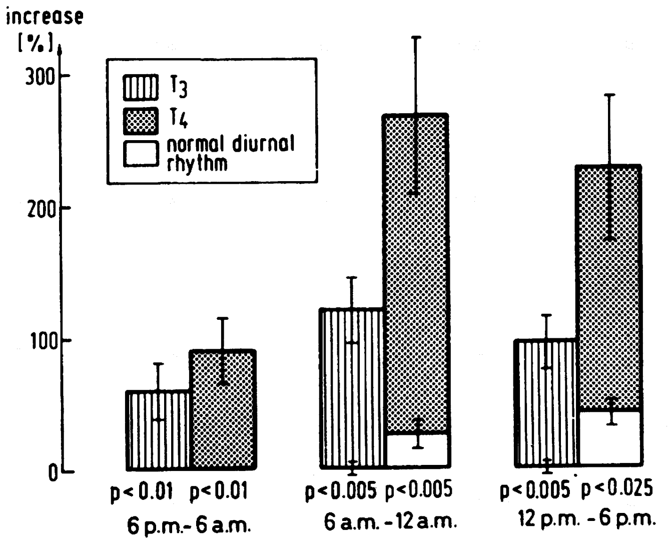

Fig. 1. Percentage increases of T_3 and T_4 excretion in urine (N=35) before 6 p.m. - 6 a.m.), during (6 a.m. - 12 noon) and after (12 noon - 6 p.m.) experimentally provoked motion sickness compared with the normal diurnal rhythm (N=11). For all samples, the percentage increase of hormone excretion was calculated in relation to the night period (6 p.m. - 6 a.m.) after the rotation experiment.

(T_3:121 ± 26%, T_4:268 ± 59%, $p<0.005$, paired Wilcoxon rank test). The thyroid hormone excretion was still elevated in the collection period after the rotation test (T_3 by 91 ± 21%, $p<0.005$, T_4 by 227 ± 55%, $p<0.025$).

The highest absolute hormone excretion observed in four persons during the 6-h collection period of the rotation experiment lay between 0.80-1.16 μg T_3 and 0.72-1.07 μg T_4. From this, a daily excretion of 3.20-4.64 μg T_3 and of 2.88-4.28 μg T_4 could be calculated. These values show clearly an excess thyroid hormone excretion, which is otherwise found only in patients with hyperthyroidism (6).

The comparison of the groups tested showed no significant differences in the thyroid hormone excretions, although the pilots removed from the duty roster excreted relatively more thyroid hormones in the rotation period (T_3: 220 ± 148%; T_4: 297 ± 113%) than the volunteers (T_3: 102 ± 23%; T_4: 227 ± 45%).

Two test persons were rotated without the provocation of the Coriolis effect (control experiment). One of these showed no change in thyroid hormone excretion during the day of the rotation test, whereas the other person showed symptoms of motion sickness with sweating and pallor during the rotation, although he did not vomit. In connection with these symptoms, the T_3 excretion increased by 71% and T_4 by 94%. These values were clearly below those of fully stressed subjects. One subject of the group of qualified pilots showed only a similar weak response during the rotation test with sweating, pallor, nausea, but without vomiting. This pilot had an increase in T_3 excretion of 16% and in T_4 excretion of 48%.

Four persons were retested in the same way after a time interval of several months for reproducibility. Three of these test persons showed a similar increase of T_3

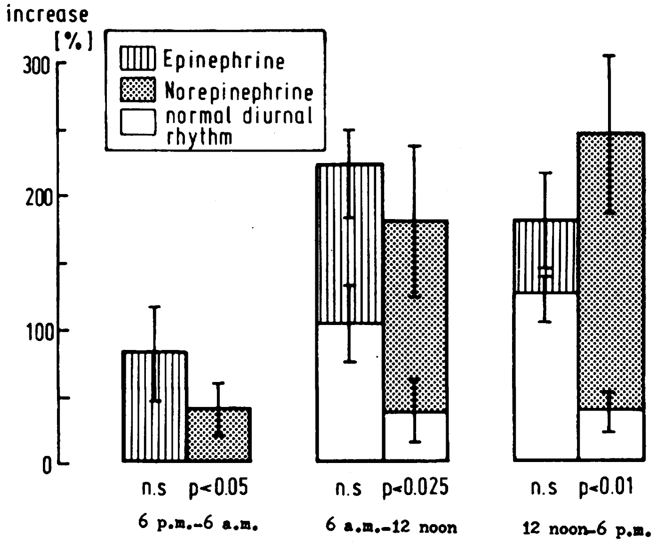

Fig. 2. Percentage increases of epinephrine and norepinephrine in urine (N=26) before (6 p.m. - 6 a.m.), during (6 a.m. - 12 noon), and after (12 noon - 6 p.m.) experimentally provoked motion sickness compared with the normal diurnal rhythm (N=10). For all samples, the percentage increase of hormone excretion was calculated in relation to the night period (6 p.m. - 6 a.m.) after the rotation experiment.

and T_4 excretion. One candidate showed little stimulation in either test.

The percentage increase of catecholamine excretion was similar to that of thyroid hormones (Fig. 2). Before the rotation test, the hormone excretion was already elevated (epinephrine by 83 ± 36%; norepinephrine by 41 ± 21%, mean ± S.E.) in comparison with the collection period during the night after rotation. In the following periods, epinephrine showed a further increase (6 a.m.-12 noon: 219 ± 41%; 12 noon-6 p.m.: 181 ± 39%) which was not statistically different from the normal diurnal rhythm. The increase of norephephrine excretion was statistically significant (6 a.m.-12 noon: 180 ± 57%, $p<0.025$; 12 noon-6 p.m.: 246 ± 61%, $p<0.01$). In the control experiment without Coriolis effect there was no significant increase of catecholamine excretion.

In spite of the similarity of urinary increase in thyroid hormones and catecholamines, no correlation between these hormones was found.

Serum determinations: Antidiuretic hormone, growth hormone, prolactin (4), and T_3, T_4, T_3U, TBG, and TSH were determined in the serum samples from the subjects submitted to the rotation experiment. Although

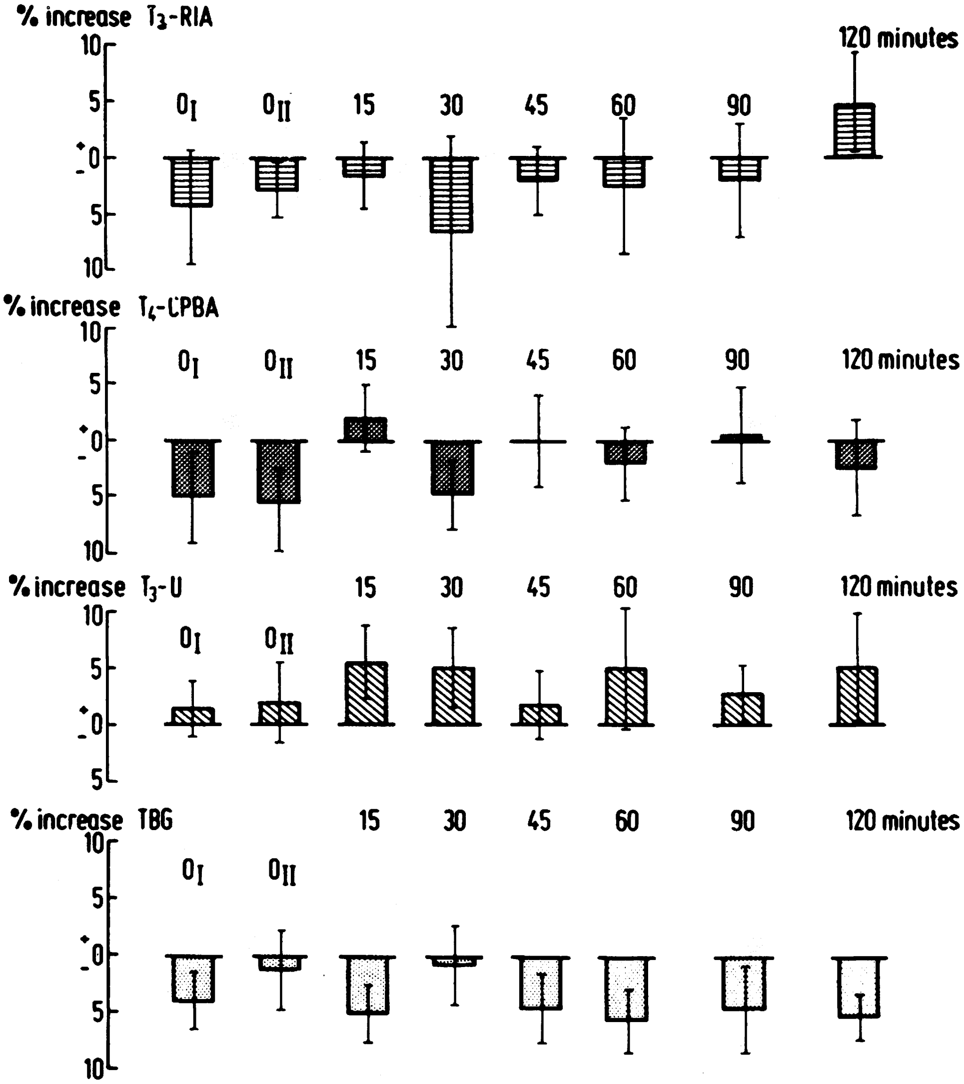

Fig. 3. Percentage increases of T_3 (N=6), T_4 (N=11), and TBG-levels (N=6) in serum and of T_3U (N=11) immediately before (OI), immediately after (OII), and 15-120 min after the rotation experiment. For all samples the percentage increase was calculated in relation to a sample taken 30 min before the rotation experiment.

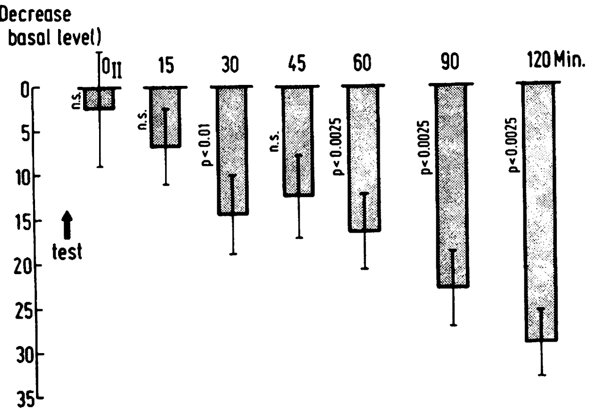

Fig. 4. Percentage decrease of TSH-levels in serum (N=23) immediately after (OII), and 15-120 min after the rotation experiment. For all samples, the percentage decrease was calculated in relation to a sample taken immediately before the rotation experiment.

the thyroxine (N=11), T_3 (N=6), T_3-uptake (N=11), and TBG levels (N=6) of all specimens showed no statistically significant individual changes during the observation period (Fig. 3), the levels of TSH in serum (N=23) decreased to a minimum of 35% of the initial value of 120 min ($p<0.0025$) (Fig. 4). During the control experiment without Coriolis effect, TSH levels remained almost constant.

DISCUSSION

Contradictory results have been reported in the literature about the possible connection between thyroid function and stress. Because of the partially similar hormonal response of catecholamines and thyroid hormones, a relationship between these two different hormone systems has been suggested for a long time. In 1949, Eickhoff described persisting thyrotoxicosis in wild rabbits induced by ferreting (2), with typical symptoms such as muscle weakness, exophthalmos, loss of weight, tachycardia, and adynamy. Galton (5) found an increased turnover and deiodination of T_4 in stressed and thyreodectomized rats, and Winder (14) a shortened half-life of thyroxine in physically stressed rats. An increased turnover of thyroxine during acute infection in monkeys was found by DeRubertis (1), and Rastogi described an increase of thyroxine excretion in urine of man during infectious disease (11). Noel (10), in contrast, found an increased release of TSH, prolactin, and growth hormone after parachute jumping, and we have now observed a significant decrease of TSH levels in serum after provocation of motion sickness.

Associated with the TSH decrease during and after the rotation experiment, an increase of thyroid hormone excretion in urine was found in this study, whereas the serum levels of T_3, T_4, and TBG, as well as T_3U remained unchanged. Because the excretion of T_3 and T_4 in urine with normal renal function depends upon the concentration of free, unbound hormones in serum (12), it may be concluded, that motion sickness effects an increase of the free hormones in serum. Apparently, this increase is too small to affect the T_3U result, but is sufficient to suppress TSH secretion. The unchanged levels of TSH and of thyroid hormone excretion in the control experiment without the Coriolis effect suggest that the change of thyroid function is, in fact, induced by motion sickness. The reproducibility of the increment of thyroid hormone excretion in the same test persons show that this excretion may be used as a further integrated measure for the quantification of stress. The results suggest that stress situations, such as motion sickness, lead, via an increase of the free thyroid hormones in serum, to their increased excretion in urine. In spite of unchanged levels of T_3, T_4, and TBG, this also effects a suppression of TSH secretion. This alteration of global function of the pituitary-thyroid axis represents a fourth independent endocrine system which may be studied—when stress-situations are to be quantitated using endocrinological techniques—taking the catecholamine response, the posterior pituitary and ADH, and the anterior pituitary with growth hormone, prolactin, and ACTH-cortisol as the other three systems.

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