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Increased Secretion of Growth Hormone, Prolactin, Antidiuretic Hormone, and Cortisol Induced by the Stress of Motion Sickness

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The stress of motion sickness was experimentally provoked by Coriolis effect. Significant and reproducible increases from the basal serum level (△ mean ± S.E.) of antidiuretic hormone (△ - ADH: 48.2 ± 4.6 pg/ml; $p<0.0005$), of growth hormone (△ - hGH: 10.0 ± 1.2 ng/ml; $p<0.0005$), of prolactin (△ - hPRL: 186.5 ± 29.9 μU/ml; $p<0.0005$), and of cortisol (△ - F: 12.3 ± 0.9 μg%; $p<0.0005$) were observed, whereas the luteinizing hormone levels did not change significantly. The stimulation of hormone secretion induced by different degrees of motion sickness seems to correlate with the severity of motion sickness. The secretion of antidiuretic hormones is the most sensitive indicator for the stress of motion sickness whereas growth hormone, prolactin, and cortisol responses to the stress of motion sickness are more delayed and less pronounced.

MOTION SICKNESS (ms) during the early stages of military flight training has been reported in 10-18% of pilots (8,15). Therefore, an attempt has been made to reduce the number of unsuitable candidates by means of tests to evaluate individual ms - susceptibility. Psychological, clinical, and physiological, but no endocrinological factors have been used to evaluate ms - susceptibility (15). Since ms represents a stress situation, we have investigated the response of pituitary and pituitary-dependent adrenal hormone secretion to experimentally provoked ms. Results of this stimulation test are presented in this paper.

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MATERIALS AND METHODS

We rotated 35 fasting male subjects clockwise in a rotary chair at 8.00 a.m. During the rotation period, the eyes of the subjects remained covered. The entire test was performed at 22°C and completed at 12.00 noon. The angular velocity of the rotary chair was increased stepwise by 15°/s up to a maximum of 215°/s. Maximal angular velocity depended on the individual number of head movements necessary to elicit frank motion sickness (fms). The latter became evident by vomiting or retching of the subject. When fms has developed, the rotary chair was stopped immediately by use of a brake, which slowed down the angular velocity by 5°/s². During the rotation period, head movements were performed rhythmically in the four cardinal directions, with 20 head movements per acceleration step. Development of ms symptoms was registered according to a numerical score described by Miller and Graybiel (12).

Blood samples were taken 30 min (-30) and immediately before (O/I) and after the rotation period (O/II), as well as 15, 30, 45, 60, 90, and 120 min thereafter. In four subjects, additional samples were collected during the rotation period in fractions over a period of 4 min using a peristaltic pump.

Urine was collected over four periods:

fraction I	(6 p.m. - 6 a.m.) before the test,
fraction II	(6 a.m. - 12 noon) including the test period,
fraction III	(12 noon - 6 p.m.), and
fraction IV	(6 p.m. - 6 a.m.), after the test period.

Serum levels of growth hormone (hGH), prolactin (hPRL), luteinizing hormone (LH), and antidiuretic hormone (ADH) were determined by radioimmunoassay (21,24). Serum and urine levels of cortisol were measured by competitive protein-binding assay (22). Blood glucose was measured by the hexokinase-method (Boehringer, Mannheim, FRG). Serum and urine osmolality were determined by freezing point reduction

TABLE I. BASAL AND MAXIMAL SERUM LEVELS OF ADH, hGH, hPRL, LH, CORTISOL, AND GLUCOSE.

	Maximal level (mean±S.E.)	Basal level (mean±S.E.)	Unitage	Significance +) ($p<0.0$)	X-fold increase	Peak time ++)	n
ADH	53.7± 4.6	2.2±6.5	pg/ml	0.0005	24.4	O/II	31
hGH	9.8± 1.2	0.7±0.1	ng/ml	0.0005	14	O/II to 30′	29
hPRL	311 ±26	147 ±7	μU/ml	0.0005	2.1	O/II to 15′	29
LH	3.1± 6.6	1.9±0.3	mU/ml	—	—	—	17
cortisol	21.3± 1.4	10.1±1.2	μg%	0.0005	2.1	O/II to 30′	29
glucose	110 ± 2.2	96 ±1.6	mg%	0.0005	1.14	O/II to 30′	23

+) significance determined between maximal and basal level by Wilcoxon test
++) peak time is marked according to the time scale of Fig. 1, 2.

(Knauer-Osmometer). Statistical analysis was performed by paired and unpaired Wilcoxon-test and the student's t-test.

RESULTS

The number of ultimately performed head movements ranged between 94 and 300; the mean was 158.7 ± 8.2. Two subjects performed 300 head movements with only slight ms symptoms and slight increases of hormone levels. No correlation was found between the number of head movements and the maximal hormone levels when calculated *for all tested subjects*. In contrast, the increase of hormone secretion correlated well to the increasing number of head movements and the increasing degree of ms *in a single subject*.

The stress of fms induced in all subjects a significant increase of ADH, hGH, hPRL, and cortisol secretion (Table I), whereas LH levels decreased slightly, but not significantly. The hGH secretion showed two separated peaks before (O/I) and after (O/II) rotation (Fig. 1). The first increase occurred in those subjects (n=7) who were already stressed by venipuncture. Three of those subjects also showed an increase of hPRL, but not of ADH or cortisol, before rotation period. The hGH increase induced by fms was still significant after the rotation period ($p<0.025$), though there was no significant difference between the hGH peak before and after rotation. Maximal levels of ADH

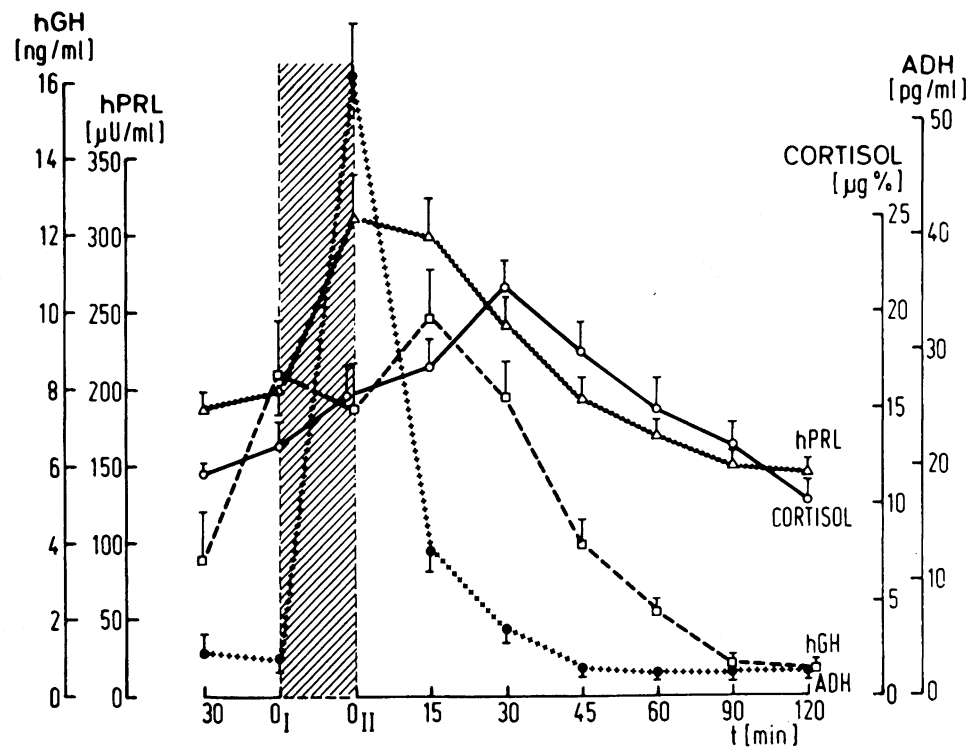

Fig. 1. Secretion of ADH, hGH, hPRL, and cortisol induced by motion sickness. ADH (closed circles), hGH (open squares), hPRL (open triangles), cortisol (open circles), vertical bars represent S.E.M. The individually different duration of rotation period (hatched area) is indicated by the dotted line between O/I and O/II which, in turn, indicates the start and stop of the rotation.

occurred practically always after cessation of rotation, whereas levels of hGH, hPRL, and cortisol rose to a maximum from immediately after (O/II) to 30 min after rotation. In four subjects, ADH secretion showed two peaks—shortly before fms became obvious and after rotation stopped (Fig. 2). In two of those subjects, the first peak was higher than the second; in the other two, this pattern was reversed. Serum osmolality was not influenced by ADH secretion. The volume of urine fraction II collected during the test period was reduced significantly ($p<0.1$- $n=29$) compared with the previous nocturnal fraction I. Urine osmolality of fraction I (618 ± 70 mosmol/1) increased to 788 ± 102 mosmol/1 in fraction II (mean ± S.E.).

Cortisol secretion (Fig. 1) induced by fms was associated with changes of the white blood cell count. The leucocytes increased significantly ($p<0.005$) from 2406 ± 557 to 3602 ± 819 ($x \cdot 10^3/mm^3$, mean ± S.E.) from the end of the rotation period until 120 min thereafter. The eosinophiles were reduced correspondingly.

The levels of blood glucose increased significantly up to 110 ± 2.2 mg% ($p<0.0005$; $n=23$) after rotation stopped compared with the basal level (96 ± 1.5 mg%, mean ± S.E.).

Urinary excretion of cortisol was not increased significantly by the stimulation test when compared to the normal diurnal cortisol excretion (22).

The reproducibility of fms-induced hormone secretion was demonstrated in four subjects, who were tested again by the described method after an interval of 3 months. ADH, hGH, hPRL, and cortisol levels in both tests showed a similar secretion pattern with similar maximal levels (Table II). Grading ms symptoms demonstrated a nearly identical development of ms symptoms in each subject retested. The number of performed head movements correlated well ($r = 0.75$, $b = 0.97$) when test and repeated test were analyzed.

TABLE II. TEST RETEST REPRODUCIBILITY OF SERUM LEVELS OF ADH, hGH, hPRL, AND CORTISOL (n = 4).

	Correlation of secretion profile (n = 32)		Correlation of maximal levels (n = 4)	
	r*	b**	r*	b**
ADH	0.96	1.06	0.95	1.12
hGH	0.81	0.70	0.70	0.89
hPRL	0.82	1.05	0.61	0.64
cortisol	0.76	0.56	0.74	1.19

* r = correlation coefficient
** b = regression coefficient (slope of the line y = a + bx)

Hormone secretion *during* the rotation period induced by fms was investigated in eight subjects (Fig. 2). In all subjects, hormone secretion was stimulated before fms occurred and increased parallel with the development of ms symptoms. Excessively high hormone levels were observed in those subjects demonstrating not only vomiting or retching but also pallor, sweating, and increased salivation. The stress of rotation without performance of head movements elicited in one of three subjects (Fig. 3) only slight symptoms of ms associated with an increase of hGH levels up to 12 ng/ml, whereas the other two subjects showed neither stimulation of hormone secretion nor ms symptoms. The hGH secretion in this one subject was stimulated up to 30 ng/ml in the previous test with head movements.

DISCUSSION

Increased secretion of hGH, hPRL, and cortisol induced by surgical or physical stress is well documented (4,9,10,13,16). Similar responses of these

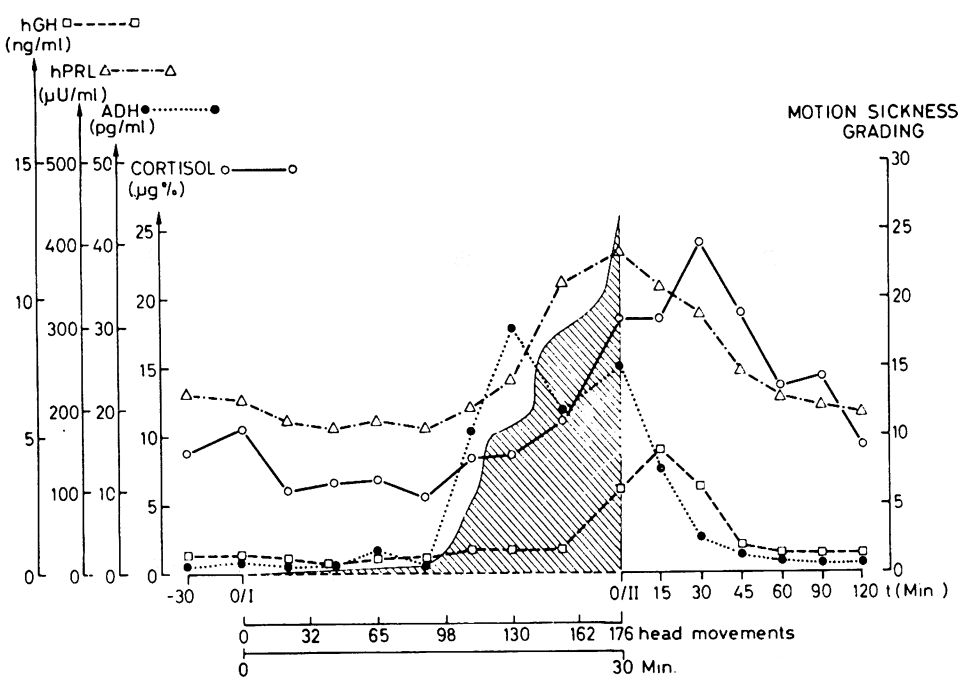

Fig. 2. Secretion of ADH, hGH, hPRL, and cortisol in a single subject during the rotation period. ADH (closed circles), hGH (open squares), hPRL (open triangles), cortisol (open circles). The hatched area represents development of motion sickness symptoms, graded on the right y-axis. The rotation period, O/I-O/II, is out of proportion in comparison with the pre- and postperiod.

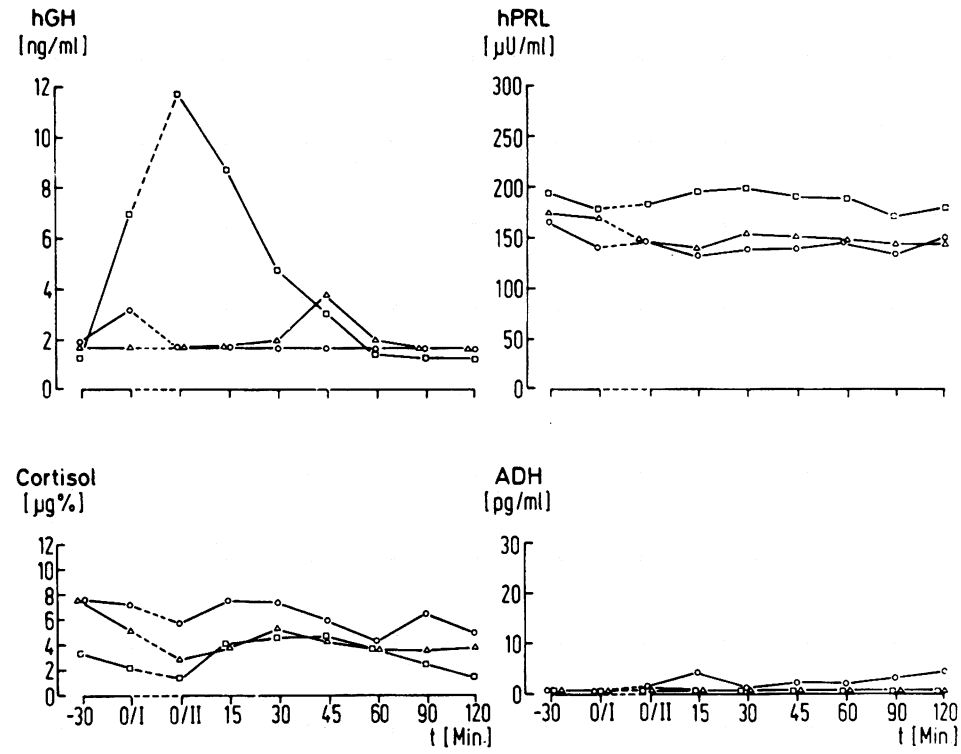

Fig. 3. Secretion of ADH, hGH, hPRL, and cortisol induced by rotation without head movements. The three subjects are indicated by different symbols (squares, circles, triangles). The individually different duration of rotation period is marked by the dotted line between O/I and O/II.

hormones to acceleration (11), aerobatic flight (18), parachute jumping (17), and rotation (1,5) have been observed. Increased serum levels of ADH in response to rotation have been described by Keil (7) using the ADH radioimmunoassay (ADH-RIA). The recent development of the ADH-RIA led to the evaluation of the role of ADH as a stress hormone. Previously, Taylor (20) had suggested an enhanced secretion of ADH leading to a decrease of urine flow in experimentally provoked motion sickness (ms). In contrast, inhibition of ADH secretion, and therefore increased urinary output, was found in weightlessness (10). Measuring ADH by bioassay, Rogge (19) reported 1967 increased ADH levels in response to acceleration. These studies suggest that ADH secretion, especially, is influenced, respectively, by the functional state of the vestibular organ and by the vestibular nuclei. The mechanism leading to ADH stimulation or suppression still remains unclear.

As shown in this study, the stress of frank motion sickness (fms) leads to a 21-fold increase of ADH levels compared with basal levels. This stimulation cannot be due to a fluid shift from the upper to the lower part of the body caused by rotation since ADH levels remain unaltered during the identical test but without head movements. Furthermore, changes in body position from a supine to an upright position provoke only slight increase of ADH levels (21). It can be concluded therefore that ADH secretion depends on the stress of ms.

In agreement with other studies (5,20,21), ms-induced ADH secretion causes a decreased urine flow associated with increased urine osmolality but unchanged serum osmolality and hematocrit. All subjects tested had no fluid intake during the test period. Thus, acute changes in ADH secretion seem to have no influence on serum osmolality, but do on urine osmolality and urine flow. But both urine parameters are indirect indicators of stress-induced secretion of ADH, since maximal urine osmolality is already reached at the presence of 5 pg ADH/ml (21).

In four subjects, ADH secretion showed two separated peaks shortly before and after cessation or rotation. The biphasic secretion seems to depend on a second stress effect induced by the acute stop of the rotary chair at O/II, following the first stress of fms. This stop effect can cause a substantial stimulation of hormone secretion alone, particularly of ADH and hGH, if the subjects develop evidence of ms symptoms after halting the rotary chair.

The fms-induced increase of hormone secretion seems to depend on the severity of fms. Those subjects who demonstrated other characteristic ms symptoms, such as pallor, sweating, increased salivation, or dizziness, before vomiting or retching had much higher hormone levels compared to those subjects demonstrating only vomiting or retching. The latter subjects seemed to be less stressed. This indicates the possibility of quantitating stress by determining hormone secretion, since subjects showing slight increases of hormone secretion experienced only slight ms symptoms. However, the hormonal response to different degrees of ms has to be investigated further to assess the reliability of individual stress quantitation by determining the secretion pattern of the different stress hormones.

Our results with experimentally induced ms demonstrate that ADH secretion is the most sensitive indicator for ms stress, whereas hGH, hPRL, and cortisol show a more delayed and less striking rise. The delay of cortisol

secretion can be explained by its dependence on ACTH. The ms-induced increase of urinary cortisol excretion was not significant. Maybe the rise of urinary cortisol was obscured by the diurnal variation of cortisol excretion. Cortisol excretion is, therefore, a less suitable parameter for stress quantitation as is the urinary excretion of catecholamines. The ms-induced changes of catecholamine excretion and of thyroid function investigated in this study have been reported separately (6). Serum levels of LH seem to be unchanged by the stress of fms. The different stress hormones respond differently to different stress stimuli (25). In our study, the effect of fms on five different endocrine systems was investigated demonstrating a characteristic pattern of pituitary hormone secretion.

The Coriolis effect is not the only stimulus for the vestibular organ leading to secretion of stress hormones. Optokinetic stimulation (3) seems to provoke the same effect. Preliminary results from our laboratory show that ADH increases slightly (Δ ADH:2.68 $\pm$ 0.68 pg/ml) after mild optokinetic stimulation with slight ms symptoms. During this test, cortisol levels increased slightly but not significantly, whereas hGH and hPRL levels did not change. In order to investigate the hormonal response to psychological stress, five subjects performed an arithmetic computation test. No differences were seen in serum ADH, hGH, and hPRL levels before and after the test. Only slight increases of ADH, hGH, and hPRL have been reported in response to other psychological test methods (15,23).

The secretion of hGH, hRPL, ADH, and cortisol induced by ms was investigated primarily to find a new test for evaluation of individual ms susceptibility. Our data indicate that the secretion of hormones depends on the individually different susceptibility for ms since the stimulated secretion correlates well with the duration of the rotation period in the individual and with the severity of his symptoms. The reproducibility of these results has been demonstrated. Thus, it is concluded that the determination of hormone secretion may prove to be helpful in predicting motion sickness susceptibility.

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