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SELF-REPORTED STRESSORS, SYMPTOM COMPLAINTS AND PSYCHOBIOLOGICAL FUNCTIONING II: PSYCHONEUROENDOCRINE VARIABLES

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Abstract—The present study examined resting endocrinological functioning and endocrine responsivity to new challenges as a function of self-reported stress load and symptomatology. Following a baseline period, four groups of male subjects (low-load/low-symptoms; low-load/high-symptoms; high-load/low-symptoms; high-load/high-symptoms) were exposed to stressful films, followed by a rest period. Blood samples were drawn after each film and after the rest condition, and urinary samples were collected during two nights preceding the experimental session. Neuroendocrine variables measured in plasma included adrenaline, noradrenaline, ACTH, cortisol, growth hormone, prolactin, and testosterone. The urinary samples were assayed for noradrenaline and adrenaline (in relation to creatinin). High-symptom subjects had significantly higher plasma levels of noradrenaline and overnight urinary adrenaline levels, whereas their cortisol levels tended to be lower as compared to the low-symptom group. The plasma noradrenaline/cortisol ratio was higher among the high-symptom subjects. However, upon controlling for neuroticism and life style factors (smoking and alcohol consumption), all but the effects on cortisol failed to meet significance criteria. Higher stress load was associated with higher plasma adrenaline responses during the laboratory session, irrespective of neuroticism or life-style measures. These results therefore suggest that in addition to measuring exposure to real-life stressors, it is also necessary to measure outcomes, such as symptoms, and to be aware of the effects of neuroticism and life-style when attempting to understand which specific psychosocial factors affect psychoendocrinological functioning.

Keywords: Stressors; Self-reported; Symptom complaints; Psychobiological functioning; Psychoneuroendocrine responses.

INTRODUCTION

Endocrine responses to stressful stimulation are hypothesized to play a significant role in enhancing disease susceptibility [1–4]. Much of the evidence providing a connection between stressor exposure and endocrine or immunological responses comes from experimental and field studies of specific real-life stressors (e.g., danger of radiation,

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workload, examinations, bereavement; for reviews, see [5–10]) or psychoendocrinological investigations with posttraumatic stress disorder (PTSD) subjects [11–15]. While exposure to these often extreme, discernable, events clearly leads to endocrinological and immunological effects, the extent to which the more diffuse self-reported stressor measures, such as life-events or daily hassles, predict those alterations is virtually unknown. The present study was specifically designed to assess resting endocrinological functioning and endocrine responsivity to new challenges as a function of self-reported stress load and symptomatology.

Following Selye's [16] original theory of stress, the assumption has tended to be that greater stress load, as found with greater numbers of negative life events, will lead to elevated levels of cortisol release. Those expected elevations have been reported by some [e.g., 17, 18], but others have yielded confusing and, at times, contradictory results [19–21]. Various theoretical reviews [e.g., 23, 24] also suggest that chronic stressor exposure is associated with normal or relatively low cortisol levels. Further inconsistencies are found when cortisol levels are assessed as a function of stress outcomes (i.e., illness). Rose and associates [25] reported the unexpected finding that higher cortisol levels were associated with lower (physical) illness rates (although those who experienced more psychiatric symptomatology had slightly higher average cortisol levels).

The pattern seen with catecholaminergic functioning looks quite different and more consistent, with raised levels apparent even during periods of rest after prolonged exposure to demanding conditions. In assessing catecholaminergic functioning, Elgerot (cited by Frankenhaeuser [26]) showed a pronounced elevation of adrenaline output in office workers during the evenings, which were spent relaxing at home, after a period of overtime at work. Meijman's group [27] reported corresponding findings in a study among driving examiners. Davidson and coworkers [28] found elevated catecholamines during both waking and sleeping hours in a sample living near the Three Mile Island nuclear power plant. However, not all that were exposed to this event showed the same levels or duration of response.

Some of the apparent inconsistency in adrenocorticoid results may be a product of adaptations occurring over time. In their review of studies on hypothalamic–pituitary–adrenal (HPA) functioning in PTSD patients, Yehuda and coworkers [13] reported the consistent finding of a suppression of the HPA axis in PTSD under baseline conditions. Additionally, research with animals has provided evidence of a gradual decrease of adrenocorticoid levels after prolonged exposure to stressful stimulation [see 12, 29], although other researchers have found the classical Selyean stress triad, including increased corticosterone levels [30].

In short, until now it remains unclear what factors determine the course of these baseline levels, although such findings do suggest that chronic exposure to stressful conditions triggers adaptive central suppressive mechanisms of cortisol release. The specific conditions under which the sampling takes place may also be relevant [24]. The PTSD studies in particular indicate, however, that decreases in baseline HPA activity do not necessarily parallel changes in mood or psychological state.

The diversity of the stress experiences of those with apparently similar load further complicate life-events research. Herbert and Cohen [9], in their recent meta-analytic review of psychoimmunology, make a direct comparison between the immunological effects of exposure to discrete objective events, such as loss experiences or examina-

tions, and the relationships between immune measures and scores on checklists of events. These authors conclude that immune alteration is greater when objective events are assessed compared to when self-reported stressors are measured. Among the explanations they put forth is one that emphasizes the proximity between the occurrence of the event and the biological determinations. It is tempting to assume that the same reasoning applies to psychoendocrine measures. For example, elevated cortisol levels have been reported among those subjected to severe, chronic stressors, such as those living near the damaged Three Mile Island nuclear power plant [31] or the Americans held hostage in Iran [32].

With extreme, discernable events, interpretations will show more homogeneity than in ones where the severity and controllability may show more diversity among those affected. Subjective emotional responses to events and their associated endocrinological results clearly lend another layer to the issue. Steptoe [33] and Antoni [34], among others, have noted the extent to which psychological distress and cognitive interpretations affect amplitude and type of subsequent biological responses. One aspect of the stress process, that is, physical symptoms, may be as much a predictor of subsequent biological responsivity as it is a marker for previous insult. Accordingly, the present study selected participants based on self-reported stress load, but also split high and low load groups on the basis of self-reported symptoms.

In the absence of discrete, objective events, it may also not be expected that a general stress load should result in baseline differences where adaptation capabilities are most likely to be adequate. One little-used approach for assessing the effects of stressor exposure is to test the responsivity to additional, controlled, acute challenges. As markers of the body's regulatory systems, patterns of further alterations among hormones can provide insight not only the into physiological status (as related to the chronic stressors) but also into the resistance against further perturbations. Dienstbier [35], for example, has stated that inadequate biological functioning is characterized by relatively high baseline levels and decreased reactivity with long recovery.

Partial support for this view comes from Schaubroeck and Ganster [36], who found consistently significant, but negative, relations among the reactivity of cardiovascular and endocrine (adrenaline and noradrenaline) measures as a function of occupational demands. Siegrist and collaborators [37] have reported similar results, finding significantly reduced heart rate and adrenaline responses to an experimental task in healthy, highly strained, subjects as compared to low work strain controls. Finally, Baum and associates [38] demonstrated a correspondence between performance measures and noradrenaline responses with employed and recently unemployed subjects showing greater persistence and task-induced catecholamine increases and more chronically unemployed subjects showing marked decreases in both performance measures and noradrenaline responses to task exposure.

Accordingly, investigations into how PTSD sufferers respond to acute challenges may be quite relevant to other studies focussing on chronic stressful conditions [39]. McFall *et al.* [14] exposed two groups of Vietnam veterans, with and without PTSD, to combat and noncombat emotional films while measuring subjective, cardiovascular, and plasma adrenaline responses. Unlike the patterns discussed above, they found larger cardiovascular and adrenaline responses to these films in the PTSD subjects. The difference may have been the result of the direct relation between the new challenge and the preexisting one. Corresponding findings were reported by Blanchard and

associates [15], who also exposed Vietnam veterans with and without PTSD to auditory stimuli reminiscent of combat. Only the PTSD group reacted with a significant 30% increase in plasma noradrenaline.

In conclusion, the picture seems somewhat complicated. While there is some evidence that PTSD subjects have higher noradrenaline/cortisol ratios [11, 12] and greater adrenaline reactivity to meaningful stimuli than controls [14, 15], there is also evidence that, under other conditions, chronic stressor exposure is associated with decreased catecholamine responsivity [35–38]. When the effects of stressor exposure in general are considered, the findings become even less consistent. By incorporating an additional measure of psychosomatic response (i.e., physical and emotional symptoms) to standard measures of stressor load, it is anticipated that greater understanding of stress-related endocrine activity can be achieved. Further, the possibly confounding roles of neuroticism [40] and life-style variables such as cigarette and alcohol use need to be taken into account.

Therefore, the present investigation focuses on the study of the relationships between symptom complaints and stressor reporting, on the one hand, and endocrine activity, on the other. Endocrine variables were measured during baseline conditions (i.e., during sleep) and during participation in an experimental session while watching stressful films representing life-relevant stressful situations. In previous research, the films have been shown to reliably elicit psychophysiological (in particular cardiovascular) and emotional responses [8, 41, 42]. A major advantage of the use of films is that there is no confounding with mental or physical effort (this in contrast to typical laboratory stressors such as mental arithmetic, Stroop-test, or reaction time tasks). In this way, both more stable and basal endocrinological functions (during sleep) as well as the ability for the endocrine system to respond to new challenges, could be evaluated. The emphasis in the present report is not on the specific effects brought about by the separate films, but rather on differences in responses to participation in the experimental session between four especially selected groups of subjects differing in self-reported load and symptoms (low-load/low-symptoms [LL/LS]; low-load/high-symptoms [LL/HS]; high-load/low-symptoms [HL/LS]; and high-load/high-symptoms [HL/HS]). Subjects were thus selected based on the extremity of their scores on stressor questionnaires and a symptom checklist.

Of particular interest is the group reporting a high load with a low level of symptoms, which may be considered the stress-resistant individuals. Traditional views would predict that low-load subjects and those with few symptom complaints should respond less to stressful stimulation than would their high-load and high symptom counterparts. According to Dienstbier's [35] conception of physiological toughness, however, one would anticipate low base rates, high reactivity, and quick recovery for stress-resistant individuals, that is, the high-load/low-symptom group. Translated to the current experimental setting, this implies relatively low night values of catecholamines and high values during the experimental session.

It was expected that our selection procedure would maximize the likelihood of observing differences between these groups. Mindful of the remarks by Watson and Pennebaker [40] that self-reports of stressors and symptoms are both strongly associated with negative affectivity or neuroticism, this factor was also taken into account.

To summarize, predictions vary depending on what position one takes. Traditionally, one expects that high-load subjects, even after controlling for neuroticism and

lifestyle variables, would have higher catecholamine output, especially during the night. Dienstbier [35], in contrast, anticipates high resting levels and diminished reactivity. In that view, high-load/low-symptom individuals would be hypothesized to show low night levels and high stressor levels. With respect to the other hormones, it was less clear what could be expected. As shown before, the literature has yielded contrasting findings with respect to cortisol. Prolactin, ACTH and hGH all can be considered stress hormones, although the reaction patterns, in particular in chronic stressful conditions, have been far less extensively studied in humans. There is some evidence that prolactin release reflects passive coping [43]. Testosterone may be expected to show lower concentrations in severely strained (i.e., high-symptom) subjects (see [8]).

METHODS

A detailed description of the subjects and the general procedures has been presented by Vingerhoets and collaborators [44]. In this paper we will restrict ourselves mainly to the details relevant to the endocrinological part of this project.

Subjects

Four groups of male subjects were selected on the basis of their current stress profiles (see [42] for a further description) to participate in this investigation: (1) low-load/low-symptoms (LL/LS; $N=23$); (2) low-load/high-symptoms (LL/HS; $N=22$); (3) high-load/low symptoms (HL/LS; $N=22$); and (4) high-load/high symptoms (HL/HS; $N=24$). The stress profiles were based on the scores on (1) the Dutch Recently Experienced Events Questionnaire (REEQ) [45] (based on the Recent Life Changes Questionnaire [46]) and the Everyday Problem Checklist (EPCL) [47, 48], as indices of psychosocial load, and (2) the Hopkins Symptoms Checklist (HSCL) to operationalize symptom levels [49, 50].

Thirteen potential candidates, for different reasons, did not accept the invitation to take part in the laboratory study. All participants received 50 Dutch guilders for their participation.

Stimuli

Subjects were exposed to 6 short (5- to 8-min) films, including 2 neutral films and 4 stressful films. The four stressful films were (1) a driving examination (DT), (2) a woman dying at home and her funeral (DB), (3) abdominal surgery after a car accident (SO), and (4) rape (RA). From previous studies, these films were all known to evoke strong psychological and psychophysiological stress reactions [8, 41–42]. During the final 10-min rest conditions, the subjects were instructed to relax while listening to music.

Endocrine measures

The plasma endocrine variables included adrenaline, noradrenaline, ACTH, cortisol, hGH, prolactin, and testosterone. For the determination of the catecholamines, 0.5-ml plasma samples were extracted according to Smedes and coworkers [51], followed by HPLC (C 18 column) and electrochemical detection. The sensitivity was 5 pg/ml for adrenaline and 1 pg/ml for noradrenaline. The interassay variations were 1.5% and 16% for noradrenaline and adrenaline, respectively.

ACTH was measured by a direct radioimmunoassay using a specific antiserum to ACTH (kindly supplied by Dr. G. B. Makara, Budapest, Hungary) and synthetic human ACTH1-39 as a standard. The sensitivity was 15 pg/ml, interassay and intra-assay variations were 7.0% and 5.2%, respectively. Prolactin was assayed by a two-site immunoradiometric assay (Medgenix, Brussels, Belgium) with a sensitivity of 0.35 ng/ml and interassay and intra-assay variations of 7.1% and 4.2%, respectively. Growth hormone was determined by immunoradiometric assay (Medgenix, Brussels, Belgium), applying MRC 1 RP as a standard. The sensitivity was 0.2 μIU/ml while interassay and intra-assay variations for this assay were 7.1% and 4.2%, respectively. Cortisol was determined by radioimmunoassay (Farmos Diagnostica, Turku, Finland), with a sensitivity of 4 nmol/L and interassay and intra-assay variations of 5.0% and 2.8%, respectively. Testosterone was also measured by radioimmunoassay (Medgenix, Brussels, Belgium). The sensitivity was 0.3 pmol/L; interassay and intra-assay variation for this determination were 8.2% and 7.6%, respectively.

Catecholamine concentrations in the urine samples were assayed by liquid chromatography with fluorescence detection and precolumn derivatization [52], with a sensitivity of 0.4 nmol/L. Interassay and intra-assay variations were 4.9% and 4.0% for noradrenaline and 7.1% and 3.2%,respectively, for adrenaline. Creatinin was determined with an Epos Analyzer (Merck, Hamburg, Germany) using a modified Jaffé

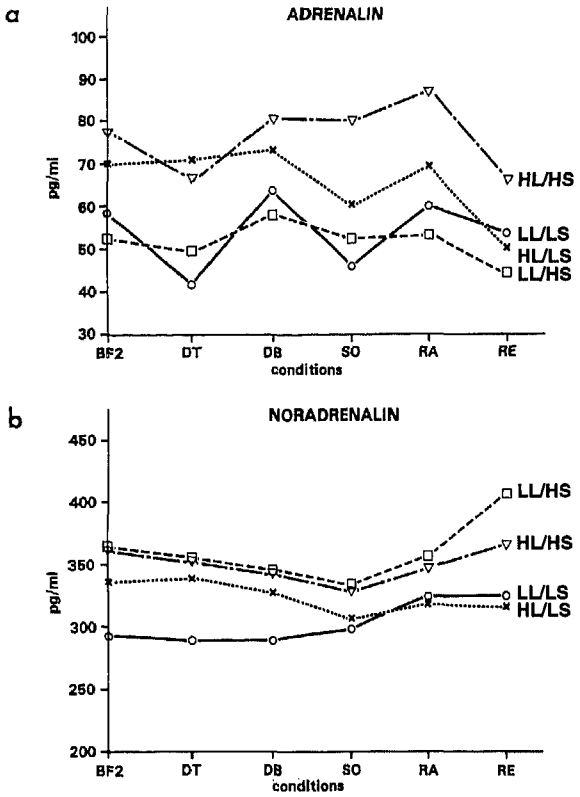


Fig. 1. Mean values of the plasma endocrine variables for the four subject groupings (LL/LS, LL/HS, HL/LS, and HL/HS), represented per condition.

procedure with Merckoled A reagents (Merck, Darmstadt, Germany). Interassay and intra-assay variations were both from 1% to 2%. Urinary catecholamine excretion is expressed as nmol per mmol creatinin.

Finally, following Mason and coworkers [11, 12], the (plasma) noradrenaline/cortisol ratios were calculated utilizing the overall means. These investigators found significantly increased ratios in a sample of PTSD subjects, illustrating the possibly more enduring psychoendocrine changes in subjects exposed to dramatic stressors.

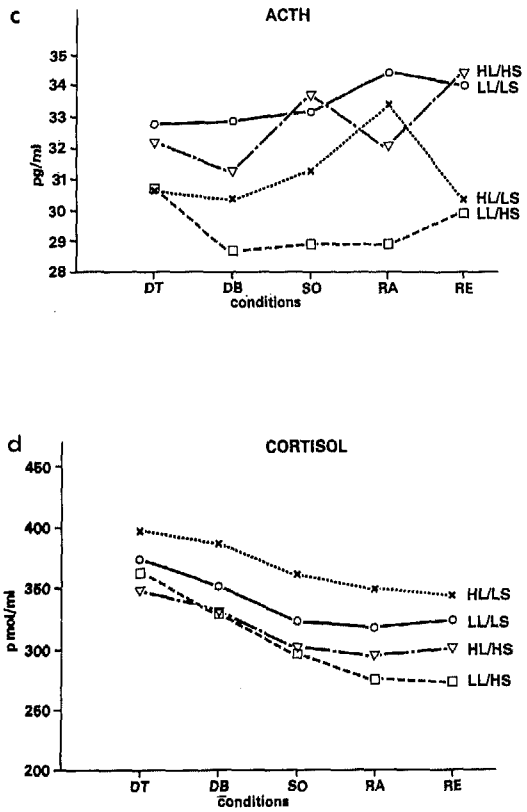
Procedures

Potential participants were visited at their homes, at which time extensive information was given about the experimental procedures and informed consent obtained. The sessions always started at 9:15 A.M. to control for circadian rhythms in the hormonal variables. Each participant voided his bladder and drank a glass of water. Subsequently, a chronical Longdwell catheter needle was inserted into an antecubital vein for blood draws that occurred immediately after each film and at the end of the rest condition. None of the subjects expressed feelings of discomfort or pain during any of the blood samplings.

The subjects received written instructions that they would be viewing 6 films depicting situations from daily life. In addition, it was emphasized that the subjects could stop their participation at any moment. When the subjects indicated that everything was clear, an adaptation period of 10 min started, followed by the initial baseline measurements. All subjects then saw the same 6 films in the same order. The session was concluded with a 10-min rest condition. A session lasted about 2 h.

Statistical analyses

For the plasma hormones, ANOVAs were carried out with psychosocial load and symptoms as main (between-subjects) factors and 7 measurement points (after each film and during the rest) as a within-subject



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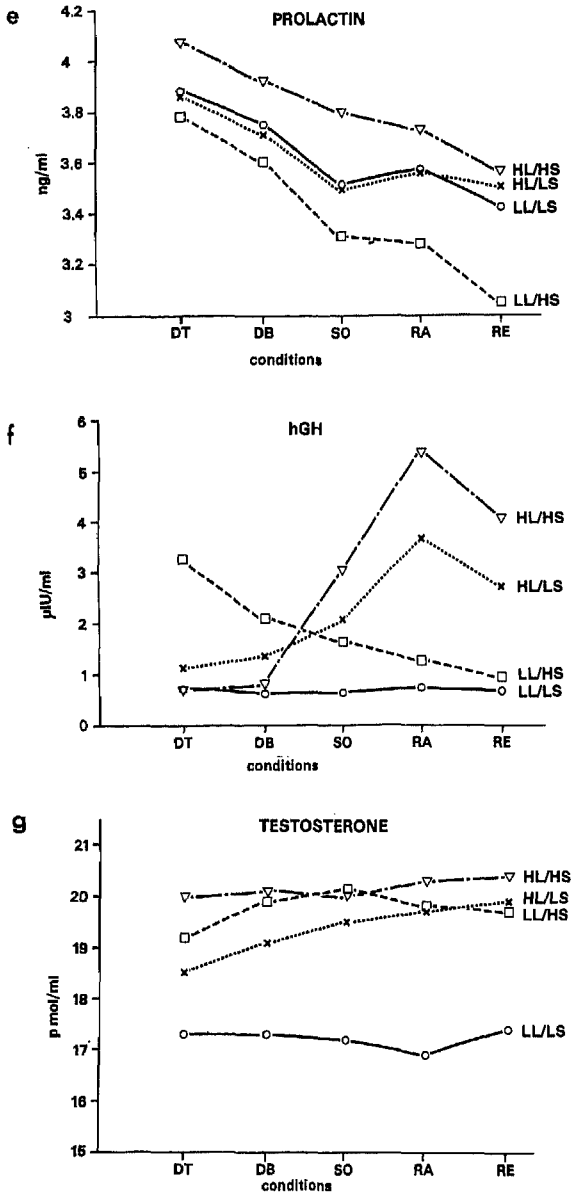
factor. ANOVAs were also run for the urinary catecholamine data, with psychosocial load and symptoms as between-subjects factors and the two nights as a within-subject factor. In addition, ANCOVAs with neuroticism, smoking and alcohol consumption as covariates were conducted. The Greenhouse-Geisser adjustments to the degrees of freedom, which provide conservative tests of the repeated measures, were applied.

RESULTS

Plasma endocrine variables

The mean hormonal levels are depicted in Fig. 1. ANOVAs revealed that those who reported many symptoms had higher noradrenaline ($F[1,85] = 3.87$, $p = 0.05$) and lower cortisol levels ($F[1,85] = 4.40$, $p<0.05$) in their plasma. Consequently, the high-symptom subjects showed significantly higher noradrenaline/cortisol ratios ($F(1, 85) = 10.04$, $p<0.01$) (see also Fig. 2).

Psychosocial load significantly differentiated plasma adrenaline levels, with individuals who reported a high load showing higher plasma concentrations of adrenaline ($F[1, 85] = 6.09$, $p<0.05$). In addition, the 'Load by Measurement point' interaction for hGH reached statistical significance ($F[1.2, 101.2] = 4.48$, $p<0.05$). Individuals reporting a high load showed an increase in hGH release towards the end of the session, whereas the low-load subjects, on average, had equal plasma levels throughout



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the session (see Fig. 1). The 'Load by Measurement point' interaction approached, but did not reach, significance for noradrenaline ($F[3.0, 255.7] = 2.54$, $p = 0.06$). For noradrenaline, post hoc analyses using Duncan's test revealed a significant drop in noradrenaline during the Rape film for HL subjects only (p values were less than 0.05).

Introduction of alcohol, cigarette use and neuroticism as covariates into the analyses yielded a different picture. With these covariates, symptom effects on noradrenaline and the noradrenaline/cortisol ratio failed to reach significance (p values were greater

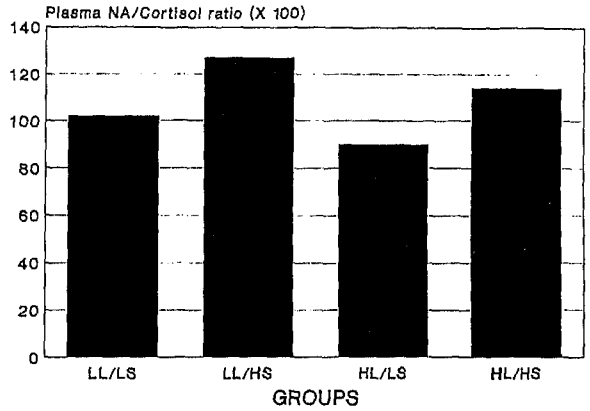

Fig. 2. Mean values of the plasma noradrenaline/cortisol ratio's endocrine variables for the four groups.

than 0.10). Symptom effects on cortisol, however, were hardly affected (main effect Symptoms ($F[1,82]=3.79$, $p=0.06$). Analyses involving Load were virtually unaffected by introduction of the covariates. Load was still found to affect plasma adrenaline levels ($F[1,82]=4.78$, $p<0.05$) and the covariates did not interact with changes over time, so the 'Load by Condition' effect on noradrenaline interactions remained intact.

Urinary catecholamines

The results of the ANOVAs for urinary catecholamine excretion indicated that high-symptom subjects produced significantly more adrenaline than did low-symptom subjects during sleeping hours ($F[1,86]=5.82$; $p<0.05$). However, this effect failed to reach significance when the covariates were added ($p>0.10$). No significant effects were found for the main factors, psychosocial load and nights, nor for the interactions (see Fig. 3). No differences between groups were found for urinary catecholamine measures obtained during the experimental session.

DISCUSSION

The purpose of the present study was to investigate the relationship between self-reported psychosocial load and symptoms, on the one hand, and endocrine functioning on the other. Two contrasting hypotheses could be tested concerning the catecholamines: Dienstbier [35] would predict low night levels and high reactivity for the stress resistant (HL/LS) group, whereas traditionally one would expect high reactivity, particularly in stress-vulnerable individuals. The results, however, fail to yield a clear and unequivocal pattern. Focussing on the urinary values, lower resting values were found for the low-symptom subjects, but (1) this held both for high- and low-load subjects, and (2) these effects disappeared after controlling for neuroticism and life style variables. The same applied to the symptom main effect of plasma noradrenaline. In contrast, the significant load effect for plasma adrenaline and the Load by Condition effect of noradrenaline were not lost. The present results thus illustrate the importance of measuring relevant confounding factors such as smoking and alcohol consumption

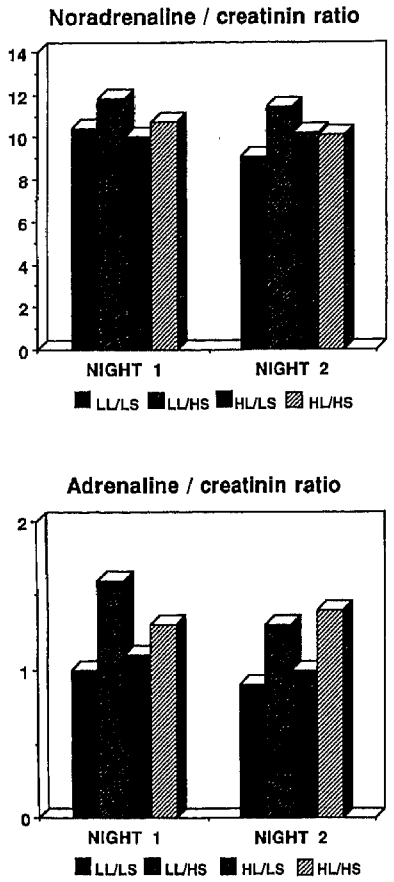

Fig. 3. Mean values of the urinary night values of adrenaline and noradrenaline, measuring during two nights preceding the experiment.

and personality attributes such as neuroticism. This pattern of findings prevents us from drawing any definitive conclusion with respect to the more or less contrasting hypotheses. Actually, neither received substantial support, after the corrections were applied.

High-symptom subjects had lower plasma levels of cortisol during the experimental sessions, thus supporting previous findings [18, 20] and some recent theoretical views [21, 22] suggesting that conditions of chronic stress as well as PTSD are characterized by relatively low cortisol levels. As already indicated, Mason and coworkers [11, 12] have identified the noradrenaline/cortisol ratio as particularly important in PTSD patients. However, the significant effect for this ratio in the present sample also disappeared with the introduction of the covariates. Our high-symptom subjects thus look like PTSD subjects until neuroticism and lifestyle variables are introduced. One may wonder to what extent adequate attention to these variables in PTSD subjects may affect previous findings.

We failed to find any main effects of psychosocial variables on 'second generation'

stress hormones such as ACTH, prolactin and testosterone. One may wonder whether this lack of association means that the effects of psychosocial factors on the pituitary are less dramatic or more labile and less enduring. Herbert and Cohen [9] have noted that studies focussing on the (immunological) effects of exposure to concrete events have generally yielded more significant associations than investigations applying life stressor questionnaires. Alternatively, it may be speculated that humans have a great potential to restore such disturbances by employing effective coping strategies. Even confrontations with severe stressors such as bereavement have failed to yield a consistent pattern of findings for these hormones. Still another possibility is that the complex interaction between exposure to chronic and acute stressors may obscure the effects on the pituitary. For example, careful study of the literature on prolactin shows that after real life stress, there is either an increase in prolactin or plasma levels are unchanged (see [53]). In contrast, after exposure to laboratory stressors (mental arithmetic, Stroop, etc.) a consistent decrease in plasma prolactin has been reported. Herbert and Cohen [9] make similar comments concerning some immune measures, in particular suppressor/cytotoxic T cells. These are consistently found to be increased following acute laboratory stressors, whereas after long-term naturalistic stressors, reliable decreases have been reported.

The failure to find significant 'Psychosocial load by Symptoms' interactions implies that our stress-resistant people (HL/LS) and stress vulnerable individuals (HL/HS) did not show reliable differences in hormonal variables. This is in contrast to the cardiovascular data collected in these same subjects [44] and to the NKCA results reported by Locke and coworkers [54]. Remarkable were the differences between high- and low-load subjects in their patterns of hGH release during the experimental session, with high-load subjects showing increases over the session and low-load subjects showing little change. These hGH findings suggest that in high-load subjects there is a closer association between hGH release and subjective distress levels (see [44]) than in low-load individuals.

Greater variation in high-load subject responses to ongoing stimuli was also observed with plasma noradrenaline. These findings together suggest that exposure to dramatic scenes indeed may elicit endocrine responses in specific vulnerable individuals. Vulnerability may then be defined as having been previously confronted with similar experiences (as in the studies exposing PTSD subjects to specific films) or subjects who, as appeared from their elevated scores on stressor inventories, are more inclined to perceive a situation as being stressful. Coupled with the PTSD studies, our findings seem to indicate that emotionally evocative stimuli may have some uses in discerning differences among stress victims. Apparently the representation of stimuli that are directly or associatively related to their stressful experiences may be optimally effective for research and perhaps for diagnostic purposes [11–15].

In conclusion, the present data strongly suggest that the mere exposure to chronic stressful conditions affects endocrine functioning, even when lifestyle factors have been taken into account. This conclusion obviously contrasts with the conclusions based on the cardiovascular findings of these same subjects [44]. From these results, we concluded that symptom levels predicted cardiovascular reactivity more strongly than did self-reported stressor levels. The present study thus makes clear that generalizing from one physiological variable to another is not justified. All physiological systems appear to have their own self-limiting adaptive mechanisms, which do not

simultaneously become active after stimulation. In addition to the different time courses and latencies of most biological variables, this prevents investigators from making adequate analyses of ongoing biological processes. Future basic research is needed to obtain a better understanding of these processes and how they interrelate.

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