Acta Derm Venereol (Stockh) 1985; 65: 199–205

Pruritus during Standardized Mental Stress

Relationship to Psychoneuroendocrine and Metabolic Parameters

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Fjellner B, Arnetz BB, Eneroth P, Kallner A. Pruritus during standardized mental stress. Relationship to psychoneuroendocrine and metabolic parameters. Acta Derm Venereol (Stockh) 1985; 65: 199–205.

The influence of experimentally-induced emotional stress on pruritic response of human skin was studied in healthy subjects. Experimental activation of the psychoneuroendocrine system was produced by standardized stressors, i.e. a colour-word-conflict test (Stroop-test) and a subsequent mental arithmetic problem. Pruritus was elicited by intradermal injection of histamine. Results obtained were compared with reported feelings of stress, and stress-induced physiological and biochemical changes. Reported stress levels were evaluated by a visual analogue scale. The physiological and biochemical observations included pulse rate, blood pressure, endocrine and metabolic parameters. The experimental model produced adequate psychoneuroendocrine stress reactions. Cutaneous responses to histamine remained despite this unaltered. The cutaneous responses were unrelated to reported stress levels as well as to physiological and biochemical variables prior to stressor exposure. The *individual* cutaneous reactions to stressor exposure were related to the adrenaline response pattern. Degree of control, ability to predict, and time limitation of the experimental situation may be important factors influencing the experimental outcome.
(Received November 23, 1984.)

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It is generally known that emotional stress may worsen pruritic disorders as well as dermatological conditions such as psoriasis (cf. 1, 2, 3, 4). Onset and relapse of itching have thus been related to stressful situations (see e.g. ref. 5). This has been substantiated experimentally by findings of lowered itch threshold, aggravation of itch intensity and prolongation of itch duration during psychic trauma (6). Furthermore, recent stressful life experience has been correlated with increased ability to detect itch and a recent history of skin disease with a lowered itch threshold (7). The precise mechanism whereby stress influences skin is however unclear. So far, emotional stressful experimental conditions, with careful observation of reported stress levels, and physiological and biochemical changes induced, has not been utilized. The purpose with this study was therefore to 1) produce a standardized, emotionally stressful situation under experimental conditions, 2) observe its influence on cutaneous (itch and flare) responses to histamine, and 3) relate these cutaneous reactions to reported stress levels as well as to physiological and biochemical observations.

MATERIAL AND METHODS

Subjects

Ten healthy male medical students, 23–42 years old, median age 30.5 years, took part in this investigation. Ascorbic acid tables (Hybrin®, Pharmacia, Uppsala, Sweden), 2 g/day, were administered orally to all subjects during one week prior to the experiment, since catecholamine excretion has been reported to be influenced by serum ascorbic acid status (8). Ascorbic acid in the dosage

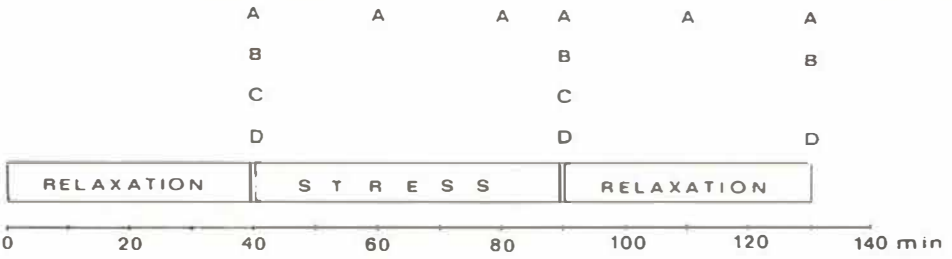


Fig. 1. Experimental design. The following abbreviations are used: A = blood pressure and blood samples, B = urinary samples, C = intradermal tests, D = stress evaluation. Pulse rate was followed throughout the experiment. For further details, see text.

utilized does not suppress histamine-evoked skin responses (9). Alcoholic beverages were not allowed for 24 hours prior to the investigation. Drugs known to interfere with the experimental tests such as aspirin, antihistamines and sedatives were eliminated one week prior to the experiment. On the day of investigation each subject refrained from smoking and drinking coffee, tea and chocolate. Breakfast at home was finished at 09.00 a.m. None of the subjects was colour-blind or had previously been exposed to the stressors used.

Experimental design

The experimental design is illustrated in Fig. 1. The experiment was conducted with the subjects sitting in a comfortable chair in front of a table and a screen except during urine sample collections. The experiment began with a pre-stress period of approximately 50 min. This was followed by a 40-min relaxation period that included listening to a 20-min tape based on Jacobsen's relaxation technique. The subjects were then exposed to mental stressors for 50 min, and were then observed for another 40 min during the recovery phase. Feelings of stress were evaluated before and after the stressor exposure as was skin reactivity to histamine. Physiological and biochemical observations were performed throughout the experiment. The investigation was performed between 10 a.m. and 1 p.m. to reduce as far as possible diurnal variations known to exist for itch threshold (6, 10) as well as for hormonal and biochemical parameters (11). The experimental design was approved by the ethical committee of the Karolinska Hospital.

Mental stressor exposure

The psychoneuroendocrine system was activated by exposing the subjects to two stressor stimuli, i.e. a colour-word-conflict test (CWT) and a mental arithmetic problem. The CWT-test is a visual-audial conflict test based on the "Stroop test" (12). The filmed version was run for 40 min. The subjects heard a voice from an accompanying sound tape reading out one of four colour adjectives (red, blue, green or yellow) in a randomized order. The voice accompanied a colour adjective word written in one of these colours randomly shown on a screen. Each stimulus was presented randomly for 0.4–1.0 sec with an interval of 0.8–1.7 sec. The subjects were requested to repond to the *colour* of the print regardless of the conflicting meaning of the word and the message of the voice. To fill out a questionnaire correctly, with all alternatives presented in a random way, is usually under such circumstances experienced as stressful. This method has thus been shown to increase urinary and plasma catecholamines (13). To augment the feelings of stress a subsequent forced arithmetic problem was administered during a 10 min period. The subjects were instructed to subtract consecutive serial 17's from 1 194 under the limited time available. The answers were given on printed forms.

Feelings of stress

Feelings of stress were evaluated prior to and following stressor exposure as well as at the end of the final relaxation period, see Fig. 1. A visual analogue scale (100 mm) was used, with end points "0" and "100" representing "not at all stressed" and "very stressed" respectively. Distance in mm from the lower (0) point was used for scoring the answers.

Physiological and biochemical variables

Urine was voided and a venflow catheter inserted in an antecubital vein when the subjects arrived at the laboratory. Urine was voided again after some 50 min whereafter urinary samples were collected and blood samples drawn with minimal disturbance of the subjects as illustrated in Fig. 1. The

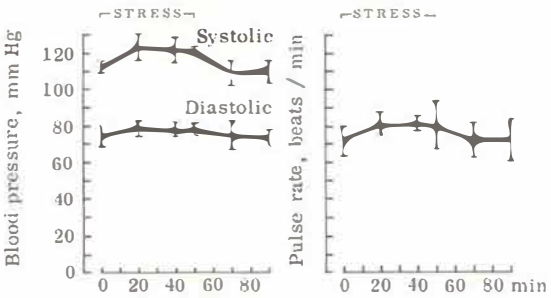


Fig. 2. Blood pressure and pulse rate (mean ± SD; $n=10$), influenced by experimental stressor exposure.

subjects drank 500 ml of tap-water after each urinary voidance. The following analyses were performed: urinary excretion of cortisol, catecholamines (adrenaline, noradrenaline and dopamine) and creatinine as well as plasma and serum levels of cortisol, growth hormone (GH), prolactin, progesterone, triglycerides, cholesterol, high density lipoprotein-(HDL)-cholesterol, glucose, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gammaglutamyltransferase (GGT), hemoglobin A_{1c}, hematocrite and cretinine. For methods utilized, see (14). Urinary excretion of catecholamines and cortisol were related to creatinine excretion. HbA_{1c} was included as a means of separating pre-existing hyperglycaemia from stress produced (11). Pulse rate was recorded with use of a photocell plethysmograph (Sanyo, Model HRM 100 E) placed on one earlobe, at 5 min interval throughout the experiment with a correlation of 0.99 between digital and manual meausurements during basal conditions. Blood pressure was recorded as illustrated in Fig. 1.

Intradermal tests

Pruritus was induced in a single blind procedure by intradermal injection of 0.01 ml of histamine hydrochloride (ACO, Solna, Sweden), 10 µg/ml. The lateral aspect of the upper arms was used. Itch duration was registered. The concomitant flare was outlined after 5 min on the skin with a marking pen and traced onto a transparent plastic film where its size was measured planimetrically. The test procedure has been thoroughly described previously (15). The skin responses were investigated both immediately before and immediately after the mental stressor exposure, as illustrated in Fig. 1. Thus, each subject was his own control in evaluation of stressor influence.

Statistical analysis

Statistical analysis between observations were performed by one-way analysis of variance (ANOVA) for correlated means. Relationships between variables were calculated using the Pearson product-moment correlation procedure.

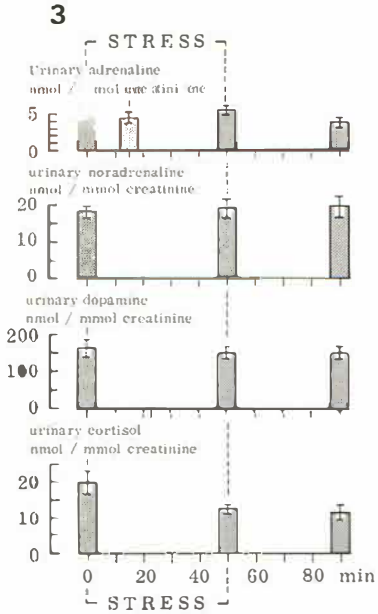
RESULTS

Feelings of stress

Reported stress level score (mean ± SEM) before stressor exposure was 16.2±5.7. After stressor exposure a significant higher level of stress feeling, 41.7±7.4, was perceived, $p<0.05$. Reported stress level declined during the final relaxation period to 8.7±2.3 units.

Physiological and biochemical data

Pulse rate, systolic and diastolic blood pressure increased during stressor exposure (Fig. 2). Urinary excretion of the two catecholamines noradrenaline and especially adrenaline increased. Urinary excretion of cortisol decreased. Plasma glucose concentration, although within the reference range, increased slightly. Serum progesterone and prolactin decreased. Stressor exposure initially decreased plasma level of growth hormone which returned to pre-stress values at the end of the stressor exposure, then declining once again. The concentration of the other biochemical variables remained unchanged. The results are presented in further detail elsewhere (14). Selected variables are illustrated in Figs. 3–4.



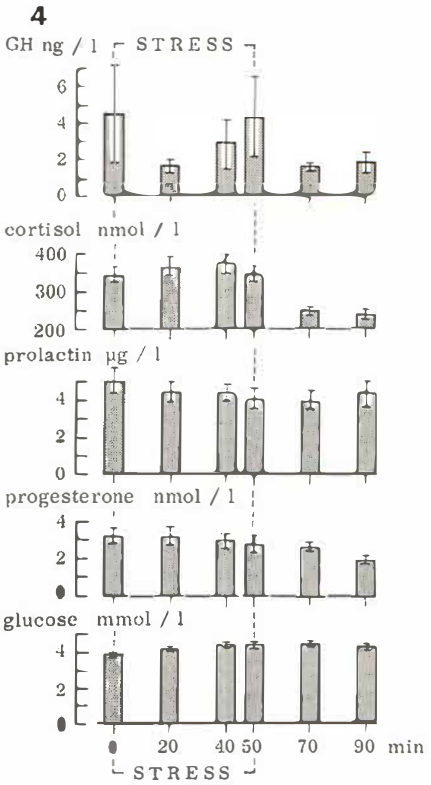


Fig. 3. Stressor influence on urinary catecholamine and cortisol excretions (mean ± SEM; $n=10$).

Fig. 4. Stressor influence on selected blood parameters (mean ± SEM; $n=10$).

Pruritic responses

Histamine-induced itch and flare responses were unrelated to reported stress levels and to physiological and biochemical variables observed prior to stress provocation, and remained unaltered after stressor exposure (Fig. 5). The *individual* cutaneous reactions to stressor stimuli were modified by the adrenaline excretion pattern, as illustrated in Fig. 6, i.e. stressor influence on urinary excretion of adrenaline was negatively correlated to cutaneous itch reactivity, $r=-0.66$, $p<0.05$, and positively correlated to concomitant flare

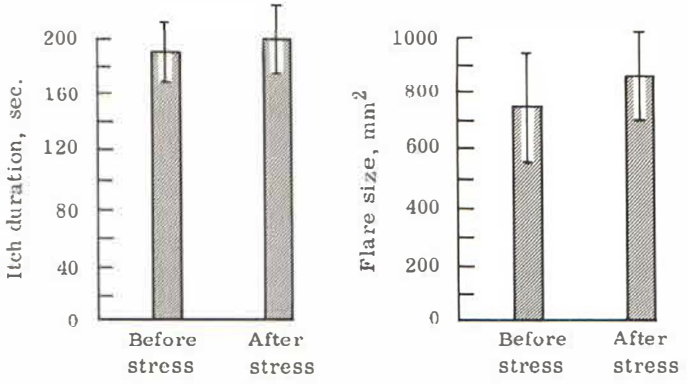


Fig. 5. Itch and flare responses (mean ± SEM; $n=10$) induced by intradermal injection, 0.01 ml, of histamine, 10 µg/ml, before and after experimental stressor provocation.

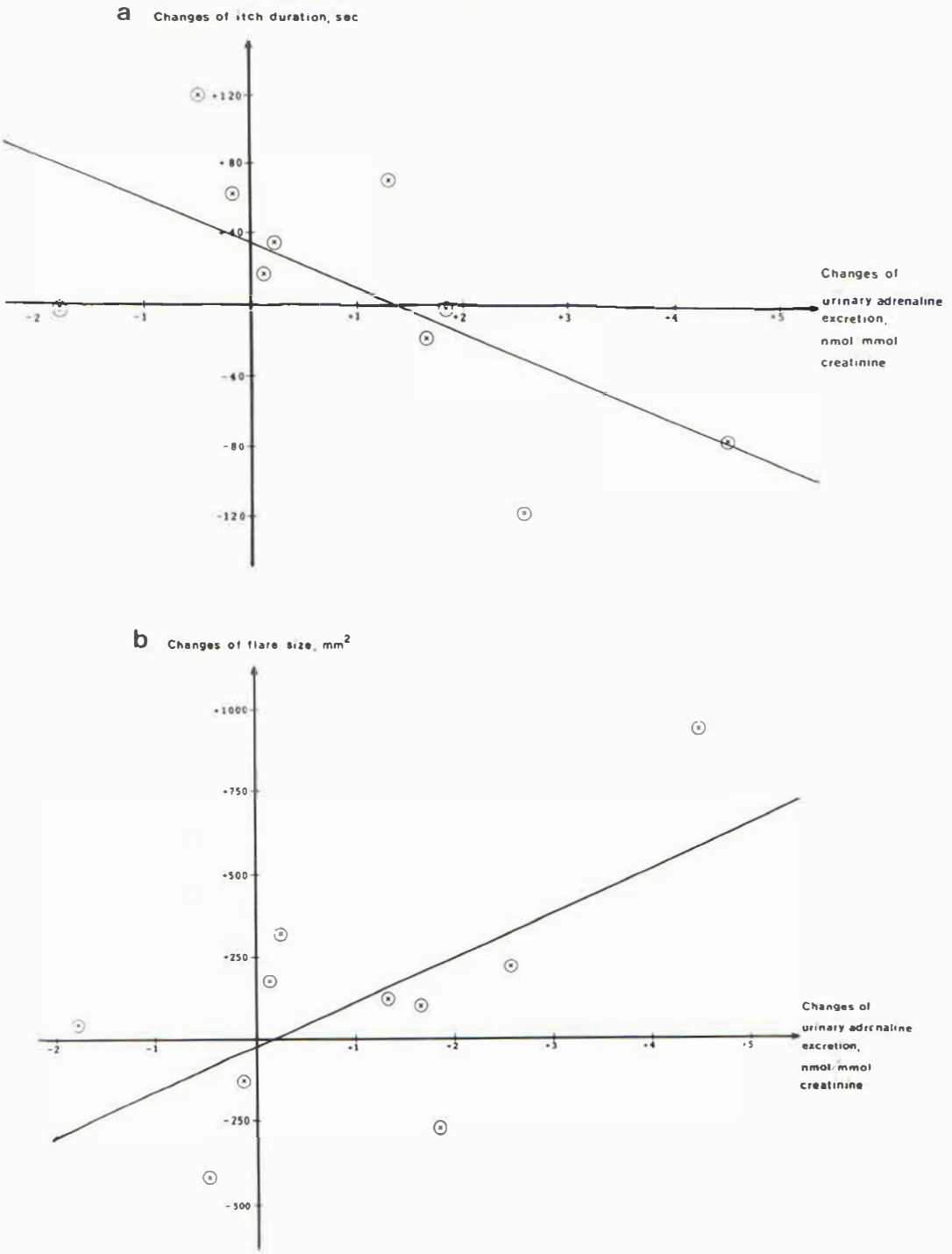


Fig. 6. Correlation between stressor-induced influence on urinary adrenaline excretion and histamine-evoked (*a*) itch, $r=-0.66$, $p<0.05$, and (*b*) flare, $r=0.64$, $p<0.05$, responses in skin. Individual data and the linear regression line are illustrated. For further details, see text.

reactions, $r=0.64$, $p<0.05$. A positive correlation was also observed between stressor influence on pulse rate and flare size, $r=0.67$, $p<0.05$. The stressor influence on cutaneous reactivity was statistically unrelated to reported stress levels and to other physiological and biochemical reactions during stressor exposure.

DISCUSSION

Adaptation to stress is partly manifested by altered activity in the psychoneuroendocrine system. Activity in the sympatho-adrenomedullary and pituitary-adrenocortical axes are thus influenced by perceived stress (13). Adequate psychoneuroendocrine stress reactions were also observed in this experiment with increased feelings of stress, increase of pulse rate and blood pressure as well as increased excretion of adrenaline in urine. Urinary excretion of cortisol, however, decreased. These findings indicate that the sympathetic-adrenal system was more selectively activated.

Exposure to mental stressors may also activate intrinsic itch modulating systems. Clinical and experimental observations thus indicate that pruritus often is provoked or enhanced in situations of mental stress (2, 3, 5, 6, 7). This is in contrast to the well-known phenomena of stress-induced analgesia (16) and may be further evidence for the idea that itch is a sensory entity that differs qualitatively from pain (cf. 15).

Despite the psychoneuroendocrine stress responses provoked in this study, skin responsiveness to pruritic stimuli remained uninfluenced. The individual cutaneous responses prior to stressor exposure were unrelated to reported stress levels as well as to physiological and biochemical parameters. Stressor influence on cutaneous reactivity was related to the *individual* urinary adrenaline response pattern, i.e. adrenaline seemed to have a depressive effect on itch (and an enhancing effect on flare) responses, in agreement with other experimental findings (17–19).

Two explanations concerning the unaltered skin reactivity during stressor exposure are considered here.

1. The experimental model utilized may be of insufficient sensitivity due to inadequate intensive properties of the stressor stimuli with a consequent inability to activate itch modulating mechanisms.

2. Another explanation worth consideration may be inability of the experimental situation as such to trigger activity in itch regulatory pathways. A laboratory setting is of limited generality, and can e.g. often be less anxiety provoking than real life situations (20). This may be illustrated in this study by the selective activation of the sympatho-adrenomedullary but not of the pituitary-adrenocortical axis, possibly reflecting perception of effort without distress (21). One important reason for this is that an experimental situation offers greater degree of control, ability to predict, and time limitation than many real events. It is of interest here to recall that stress-induced analgesia involves opioid as well as non-opioid pathways, and that opioid pathways may be selectively activated in uncontrollable, and non-opioid pathways in controllable, situations, for ref. see (16). Further, it is shown that opioid peptides enhance itching (22) while pain is suppressed. It is therefore reasonable to assume, although much remains to be learned, that a stressful, uncontrollable, unpredictable and timewise unlimited real life situation might activate opioid pathways and consequently potentiate pruritus, thereby explaining the dual effect of stress on pain (analgesia) and itch (enhancement). An investigation is under progress to elucidate this tentative hypothesis.

ACKNOWLEDGEMENT

We are indebted to Aleksander Perski, Ph.D. for excellent assistance with data analysis and to Birgitta Eriksson and Britt-Marie Pallin for skillful assistance with data collection. This project has

been sponsored by grants from the Karolinska Institute, the Edvard Welander Foundation, the Finsen Foundation and the Swedish Society of Medical Sciences.

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