

Urinary Monoamine Metabolites as Indices of Mental Stress in Healthy Males and Females

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FRANKENHAEUSER, M., U. LUNDBERG, M. RAUSTE VON WRIGHT, J. VON WRIGHT AND G. SEDVALL. *Urinary monoamine metabolites as indices of mental stress in healthy males and females.* PHARMACOL BIOCHEM BEHAV 24(6) 1521-1525, 1986.—Concentrations of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA), the dopamine metabolite homovanillic acid (HVA) and the noradrenaline metabolite 4-hydroxy-3-methoxyphenyl glycol (HMPG) were determined in urine samples from healthy male and female students by mass fragmentography. Urine samples were obtained after a demanding examination (mental stress) and a day of ordinary school work (control condition). Self-ratings were obtained of feelings induced by the examination, and of habitual psychosomatic symptoms. The results for both sexes showed that the examination stress induced a significant increase of HVA and HMPG excretion, but not of 5-HIAA. The males excreted significantly more of each of the metabolites than the females. The pattern of correlations between metabolite levels and psychological and psychosomatic variables were strikingly different for the two sexes.

5-HIAA HVA HMPG Male and female humans Urine Mental stress

WHILE the role of the catecholamines adrenaline and noradrenaline as indicators of stress induced by environmental demands has been firmly established (see e.g., [3]), less is known about the monoamines in this regard. The same is true for sex differences in stress reactions (see e.g., [4]).

The aim of the present investigation was to determine the sensitivity of monoamine metabolites as indices of mental stress in healthy males and females. The study forms part of a larger project concerned with psychoneuroendocrine stress responses in healthy males and females at different stages of development. Earlier reports in the series have focused on the urinary excretion of the catecholamines adrenaline and noradrenaline during examination stress and ordinary school work [5, 8, 9]. In the present study, the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA), the dopamine metabolite homovanillic acid (HVA) and the noradrenaline metabolite 4-hydroxy-3-methoxyphenyl glycol (HMPG) were measured by mass fragmentography in urine samples collected in a previous study of examination stress [5]. Metabolite excretion during the examination (mental stress) and a day of ordinary school work (control condition) were compared. Relationships were also examined between metabolites and stress-induced subjective reactions as well as habitual psychosomatic symptoms.

METHOD

Subjects and General Procedure

Subjects. Subjects were 30 female and 19 male high school students from Helsinki. Their ages ranged from 18 to 19 years (mean=18.8 for the females, 18.9 for the males). The body weight of the females ranged from 46 to 65 kg (mean=55.9) and that of the males from 55 to 86 kg (mean=72.4). (Mean height for the females 164.3 cm, for the males 181.9 cm.) All subjects were recruited from a longitudinal study [7] and had been examined at the ages of 11, 13, 15 and 18 years.

Examination day. Passing the matriculation examination is a compulsory requirement for students seeking admission to the university and the individual's future career may thus depend on the outcome. Consequently, the examination is generally considered a severely stressful event. It started at 9 a.m. and ended at 3 p.m. Although the students were allowed to leave earlier if they had finished their essay writing, most of them chose to stay to the end of the 6-hr period. Upon arrival in the school the subjects were asked to void and the exact time was noted. The total urine volume produced during the examination was collected. Some subjects (17 females and 15 males) voided only at the end of the examina-

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TABLE 1
MEANS AND STANDARD ERRORS FOR URINARY MONOAMINE METABOLITES IN 19 MALE AND 27 FEMALE STUDENTS DURING A STRESSFUL EXAMINATION AND DURING A DAY OF ORDINARY SCHOOL WORK; *p*-VALUES BASED ON *t*-TESTS FOR DIFFERENCES BETWEEN SEXES (INDEPENDENT TESTS) AND CONDITIONS (DEPENDENT TESTS)

	Examination day		Ordinary school day		Examination vs. ordinary school day <i>p</i> -level
	Mean	SE	Mean	SE	
5-HIAA (nmol/min)					
Females	11.0	1.3	11.3	1.3	n.s.
Males	27.9	5.6	19.3	2.5	n.s.
males vs. females <i>p</i> -level	<0.01		<0.01		
HVA (nmol/min)					
Females	16.9	1.0	13.4	0.9	<0.05
Males	27.8	2.9	21.1	2.1	<0.05
males vs. females <i>p</i> -level	<0.001		<0.01		
HMPG (nmol/min)					
Females	7.1	0.3	5.7	0.4	<0.001
Males	11.2	0.9	8.3	0.7	<0.01
males vs. females <i>p</i> -level	<0.001		<0.01		
Adrenaline (pmol/min)					
Females	10.3	1.0	8.1	0.8	<0.05
Males	19.9	1.8	11.4	1.1	<0.001
males vs. females <i>p</i> -level	<0.001		<0.05		
Noradrenaline (pmol/min)					
Females	33.2	3.1	28.3	2.2	<0.05
Males	40.4	3.0	33.2	2.0	<0.05
males vs. females <i>p</i> -level	n.s.		n.s.		

Mean catecholamine levels, reported by Frankenhaeuser *et al.* [5], are given for the sake of comparison.

tion, while the others voided once or more during it. In the latter case, each urine sample was analyzed separately. Since there were no marked differences between successive samples across the time period, the mean value for the entire period was used for each subject in the final statistical analysis.

Ordinary school work. This was the control condition, during which the subjects attended lessons on an ordinary school day ten days after the examination. They voided upon arrival at school at 9 a.m., the time was noted, and urine samples were collected 2–3 hours later.

Measures of monoamine metabolites. The total urine volume of each sample was measured and all samples were stored at -18°C . The monoamine metabolites 5-HIAA, HVA and HMPG were analysed by a massfragmentographic method [10].

Psychological Variables

Responses to the examination. Self-ratings of the subjective state prior to and during the examination were obtained immediately after the examination [9]. Discomfort scores were based on estimates of discomfort, tension and apprehension, including bodily symptoms such as heart beat, sweating, tremor and headache. Sense of success scores were based on ratings of feelings of success versus failure

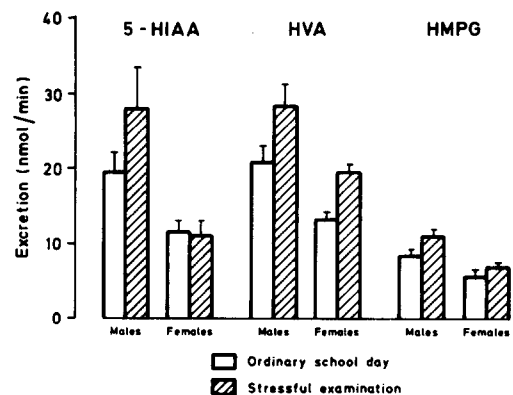


FIG. 1. Means and standard errors for urinary metabolite excretion in healthy males and females during a stressful examination and a day of ordinary school work.

TABLE 2
CORRELATIONS BETWEEN URINARY MONOAMINE METABOLITES, AND BETWEEN METABOLITES AND CATECHOLAMINES IN URINE

	Males (n=19)		Females (n=27)	
	Examination day	Ordinary school day	Examination day	Ordinary school day
5-HIAA/HVA	0.81†	0.15	0.27	0.52†
5-HIAA/HMPG	0.60†	-0.26	0.14	0.44†
5-HIAA/Adr	-0.24	-0.18	0.20	0.42*
5-HIAA/NA	0.24	0.15	0.05	0.23
HVA/HMPG	0.58*	0.34	0.17	0.59†
HVA/Adr	-0.19	0.53*	0.39*	0.34
HVA/NA	0.12	0.22	0.19	0.48†
HMPG/Adr	0.12	0.45*	0.28	0.58†
HMPG/NA	0.76†	0.71†	0.61†	0.64†

* $p < 0.05$.

† $p < 0.01$.

and satisfaction versus dissatisfaction with one's own performance. Effort and distress were measured by self-ratings of a number of variables as described earlier [6]. On the basis of factor analysis, a distress score and an effort score were calculated for each subject.

Habitual somatic discomfort. Habitual somatic discomfort was determined using a questionnaire developed for the longitudinal study [8] from which the present subjects were recruited. The questionnaire consists of 17 five-point rating scales (the response alternatives on each scale ranging from "very frequent" to "hardly ever") concerning discomfort relating to: (a) gastrointestinal functions, (b) eliminative functions, (c) swallowing and breathing, (d) dry mouth and cough, (e) heart beat and pains in the chest, (f) headache and feelings of faint, and (g) pains in the limbs. The "discomfort scores" for each of these symptom areas were added to yield a sum score.

RESULTS

Monoamine Metabolite Excretion

Comparison between stress and control conditions. Mean excretion rates for urinary metabolites during the examination day and during the ordinary school day are shown in Fig. 1 and Table 1. Mean catecholamine values reported earlier [5] are included in the table for comparison. It is seen that HVA and HMPG were significantly elevated during the examination in both males and females, and that 5-HIAA was slightly, but not significantly, elevated in the males.

Comparison between males and females. The males had significantly higher excretion rates of HVA, HMPG and 5-HIAA, both during the examination day and during the ordinary school day (Fig. 1 and Table 1).

Correlations between metabolites and body height and weight. Correlations were calculated between monoamine metabolite excretion on each of the two days and body weight and height. Only three correlations reached significance. In males, 5-HIAA during the ordinary school day was negatively correlated with body weight ($r = -0.45, p < 0.05$) and height ($r = -0.59, p < 0.05$). In the females, HVA during the

examination day was positively correlated ($r = 0.38, p < 0.05$) with body weight.

Correlations between metabolites and catecholamines. Table 2 shows intercorrelations between the three metabolites, and correlations between each of the metabolites and each of the catecholamines. During the examination all metabolites were significantly positively correlated with each other in the males, but not in the females. Conversely, during the ordinary school day the three metabolites were significantly correlated in the females but not in the males.

Correlations between noradrenaline and HMPG excretion were consistently high. Three correlations (out of eight) between catecholamine and HVA excretion were significant and one between adrenaline and 5-HIAA.

Correlations between metabolite values from the examination day and the ordinary school day tended to be positive but low, and reached significance only for HMPG in females.

Correlations Between Monoamine Metabolites and Psychological Variables

Table 3 shows correlations between metabolite values and self-ratings and performance during the examination day. In the females, significant positive correlations ($p < 0.01$) were obtained for HVA excretion and self-reported discomfort and distress. In the males, 5-HIAA as well as HVA excretion were significantly positively correlated ($p < 0.01$) with self-reported effort. In females, habitual somatic discomfort was significantly negatively correlated ($p < 0.05$) with 5-HIAA excretion.

Table 3 also shows correlations between psychological variables during the examination day and the difference in metabolite values between the examination day and the ordinary school day. In the females, increase in 5-HIAA excretion during the examination was negatively correlated ($p < 0.05$) with sense of success. In the males, increase in 5-HIAA was positively correlated ($p < 0.05$) with self-reported effort. In females, habitual somatic discomfort was significantly negatively correlated ($p < 0.01$) with increases in 5-HIAA excretion, i.e., high discomfort was associated with suppression of 5-HIAA levels as compared with the ordinary school day.

TABLE 3
CORRELATIONS BETWEEN PSYCHOLOGICAL VARIABLES AND URINARY MONOAMINE METABOLITES DURING (A) EXAMINATION STRESS, AND (B) CHANGE IN METABOLITE EXCRETION FROM ORDINARY SCHOOL DAY TO EXAMINATION

Psychological variable	During examination			Change from ordinary school day		
	5-HIAA	HVA	HMPG	5-HIAA	HVA	HMPG
Discomfort						
Females	0.14	0.51 [†]	0.13	0.10	0.27	0.30
Males	-0.14	-0.03	0.10	0.17	-0.07	-0.07
Distress						
Females	0.23	0.62 [†]	-0.03	0.31	0.50 [†]	0.10
Males	-0.12	0.03	-0.08	0.04	0.39	0.12
Sense of success						
Females	-0.38*	-0.45*	-0.22	-0.42*	-0.29	-0.39*
Males	0.29	0.37	0.17	-0.39	0.30	0.47*
Effort						
Females	0.00	0.04	0.22	0.12	0.24	0.28
Males	0.58 [†]	0.64 [†]	0.12	0.61*	0.46*	0.14
Habitual somatic discomfort						
Females	-0.37*	0.03	-0.09	-0.60 [†]	-0.04	-0.33
Males	-0.17	0.04	-0.23	-0.13	-0.06	-0.21
Performance in exam						
Females	0.30	0.13	-0.02	0.06	-0.10	-0.05
Males	0.19	0.42	0.33	-0.01	0.25	0.41

* $p < 0.05$.

[†] $p < 0.01$.

Females Whose Adrenaline Excretion Did Not Increase During Stress

In the earlier study [5], in which the present urine samples were collected, 12 females were found to be "non-reactive" i.e., they did not respond with adrenaline increase during examination stress. These females were compared with the "reactive" females in terms of monoamine metabolite excretion (increase vs. no increase) during the examination. Using a chi square test, it was shown that the females who were "non-reactive" in terms of adrenaline output tended to be "non-reactive" also in terms of HVA ($p < 0.05$) and 5-HIAA ($p < 0.01$). In other words, those females whose adrenaline output did not increase during the examination showed a lesser increase in HVA and 5-HIAA than the other females.

COMMENT

The results from our long term project show different psychological as well as endocrine response patterns for the two sexes. In general, males tend to report feelings of confidence and effort during examination stress, and their adrenaline output tends to be markedly elevated. In contrast, females often report feelings of discomfort and lack of confidence in their own performance, and their adrenaline output tends to be only moderately elevated. However, there are no marked sex differences in the actual performance level. About one third of the females in the present study did not increase their adrenaline excretion during stress [5]. This group differed psychologically from the other females in that they were oriented toward a traditional "feminine role" rather than toward intellectual achievement.

The present results showed that excretion of both HVA and HMPG was significantly higher during the stressful examination than during the ordinary school day. Males excreted significantly more 5-HIAA, HVA and HMPG than the females, both during the examination and during the ordinary school day. This is consistent with sex differences in metabolites in urine reported earlier [11]. Thus, the pattern is the same for the urinary monoamine metabolites as for adrenaline, both in terms of reactivity to mental stress and in terms of sex differences in reactivity.

It is interesting to compare the result from studies in which metabolites have been determined in CSF and urine, respectively. Studies of depressed patients show, that the concentrations of 5-HIAA and HVA in CSF tend to be lower in depressed patients than in healthy control subjects [1]. In depressed patients treated with chlorimipramine [2], the CSF level of 5-HIAA decreased while the urinary excretion remained unaffected. This suggests that measurements in CSF and urine reflect different aspects of serotonin metabolism. With regard to HMPG, however, a significant positive correlation has been reported between measurements in urine and CSF in healthy males [11]. This supports the hypothesis that the HMPG excreted in urine reflects the metabolism of noradrenaline in the brain. It is also interesting that the HMPG excretion was significantly elevated in healthy males with a positive family history of psychiatric morbidity [11].

Although there is no evidence for a relationship between central and peripheral monoamine metabolism (except perhaps for HMPG), the present results suggest that urinary monoamine metabolite levels, at least HMPG and HVA excretion, provide sensitive indices of the mental stress induced by environmental demands.

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