Cerebrospinal Fluid Levels of Monoamine Metabolites

A Preliminary Study of Their Relation to Menstrual Cycle Phase, Sex Steroids, and Pituitary Hormones in Healthy Women and in Women with Premenstrual Syndrome

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The cerebrospinal fluid (CSF) levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), and the dopamine metabolite homovanillic acid (HVA) were measured in a group of drug-free non-depressed women with premenstrual syndrome (PMS) (late luteal phase dysphoric disorder) (n = 13) and in controls with no premenstrual complaints (n = 13). In six patients and eight controls, CSF samples from both the luteal and the follicular phase were obtained, whereas in the remainder of the subjects, samples from either the follicular phase (patients: 4, controls: 2) or the luteal phase (patients: 3, controls: 3) were taken. The following observations were made: (1) Neither in the follicular phase nor in the luteal phase did the mean concentrations of CSF monoamine metabolites in the PMS group differ from the corresponding values in the control group. (2) Neither in the PMS group nor in the control group did the mean concentrations of monoamine metabolites in CSF samples obtained in the luteal phase differ from the corresponding values obtained in the follicular phase. (3) The intraindividual, intersample variations of CSF HVA and 5-HIAA concentrations were significantly smaller in the PMS group than in the control group. (4) CSF HVA correlated strongly to CSF 5-HIAA in the luteal phase of both patients and controls whereas in the follicular phase, particularly in controls, this correlation was much weaker. (5) In the luteal phase, the CSF HVA/5-HIAA ratio correlated negatively to serum levels of estradiol, progesterone, and testosterone. (6) The CSF HVA/5-HIAA ratio was significantly lower in PMS patients than in controls. (7) A positive correlation between CSF MHPG and serum luteinizing hormone was observed in the follicular phase. (8) A positive correlation between CSF HVA and serum prolactin was observed in the luteal phase. Because the study was comprised of a small number of subjects, the reported findings until replicated should be interpreted with caution.

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The premenstrual syndrome (PMS), or late luteal phase dysphoric disorder (LLPDD), is characterized by a cluster of symptoms that appear in the luteal phase of most menstrual cycles and which disappear within a few days after the onset of menstruation. Among the mental symptoms, irritability, depressed mood, and carbohydrate craving are some of the most prominent (Frank 1931; Halbreich et al. 1982; American Psychiatric Association 1985).

On the basis of both animal experiments and clinical studies, serotonin is attributed as being important for the regulation of mood, impulse control, and carbohydrate craving (for ref, see Eriksson and Humble, 1991); moreover, serotonin activity has been shown to be influenced by variations in the serum concentrations of sex steroids (see, e.g., Engel et al. 1979; Sietniks et al. 1983; Long et al. 1983; Battaner et al. 1987; Bitar et al. 1991). Consequently, the hypothesis that alterations in serotonergic neurotransmission may be involved in the pathophysiology of PMS is not unfeasible. Support for this assumption has been obtained from recent studies showing that premenstrual complaints can be markedly reduced by serotonin reuptake inhibitors (Eriksson et al. 1990; Rickels et al. 1990; Stone et al. 1991; Menkes et al. 1992; Sundblad et al. 1992; Wood et al. 1992; Sundblad et al. 1993).

Based upon the assumption that the concentrations of a certain monoamine metabolite in the cerebrospinal fluid (CSF) may reflect the turnover of the corresponding transmitter in the brain (Modigh 1975; Scheinin et al. 1986; Stanley et al. 1986), many studies have been undertaken in which CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the dopamine metabolite homovanillic acid (HVA), and the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), have been measured in psychiatric patients and in controls. A negative correlation between aggression and poor impulse control vs CSF 5-HIAA levels is one of the most replicated findings in these types of studies (Brown et al. 1982; Lidberg et al. 1985; Åsberg et al. 1986b; Brown and Linnoila 1990); in addition, some workers have found low CSF 5-HIAA concentrations in subgroups of depressed patients (Åsberg et al. 1984; Gibbons and Davis 1984; Westenberg and Verhoeven 1988). The latter finding is, however, still a matter of controversy (for refs, see Gjerris et al. 1988; Reddy et al. 1992).

As a consequence of the strong positive correlation between CSF levels of HVA and 5-HIAA usually observed, the CSF HVA to 5-HIAA ratio has recently attained increased attention as a putative marker of the interactions between dopamine and serotonin in brain (Ågren et al. 1986; Roy et al. 1986; Ågren et al. 1988; Hsiao et al. 1993; Potter and Manji 1993). Interestingly, recent studies indicate that a low HVA to 5-HIAA ratio is a more reliable marker of depression than is a low CSF 5-HIAA (for references see Reddy et al. 1992).

To our knowledge, CSF monoamine metabolites in PMS have previously been investigated in one study only (Parry et al. 1991), in which no healthy controls were included. The present pilot study had three main purposes. First, to investigate whether PMS, like some other conditions characterized by depressed mood and/or impaired impulse control, is associated with abnormal CSF levels of 5-HIAA and/or HVA, or with an abnormal HVA to 5-HIAA ratio. Second, to examine to what extent CSF monoamine metabolite concentrations, in PMS patients as well as in healthy controls, are influenced by menstrual cycle phase. Third, to explore possible relationships between CSF monoamine metabolite concentrations and serum levels of gonadal and pituitary hormones.

MATERIALS AND METHODS

Women with premenstrual irritability and/or depressed mood were recruited for a drug trial (the results will be presented elsewhere) by means of a newspaper advertisement, followed by a brief telephone interview, and a subsequent, extensive, structured interview. The primary inclusion criteria were severe irritability and/or depressed mood starting regularly around ovulation or during the two weeks preceding the menstrual bleeding and terminating within a few days after the onset of menstruation as reported by the patient during the interview. In addition, the criteria of LLPDD according to DSM-III-R (American Psychiatric Association 1985; Swedish translation), should be fulfilled. The diagnosis of premenstrual syndrome was confirmed by means of daily self-rating during two consecutive menstrual cycles using a visual analogue scale; subjects not presenting at least a 100% increase in irritability or depressed mood during the five days preceding the menstrual bleeding as compared to the mean rating of cycle days 6 to 10 were not included in the study.

Female controls, of similar age as the patients, were recruited mainly from the staffs and students at the hospital and research unit where the investigations were undertaken. In structured interviews, all controls reported a complete lack of cycle-related changes in mood. That they were free from a premenstrual increase in irritability or depressed mood was also confirmed by one month of daily self-rating.

Totally, 13 patients and 13 controls were included in the study. The mean age of the patients was 39 years (range: 29–45) and the mean age of the controls was 35 years (range: 27–43). In six patients, a CSF sample was obtained both between day 5 and day 8 of the menstrual cycle (day 1 being the first day of menstruation)

(follicular phase) and within 5 days before the expected onset of menstruation (the late luteal phase) whereas from the other seven patients, a sample was obtained in either the follicular phase (n = 4) or in the late luteal phase (n = 3). In eight controls, a CSF sample was obtained both in the follicular phase and in the luteal phase whereas from the other five patients, a sample was obtained in either the follicular phase (n = 2) or in the late luteal phase (n = 3).

The puncture was performed at 8:00 A.M. before any food intake and with the patients in bed in a recumbent position. Twelve ml of CSF were obtained and divided into 2-ml portions. 5-HIAA, MHPG, and HVA were measured using a mass fragmentographic method as previously described (Gjerris et al. 1987; Swahn et al. 1976). All samples were analyzed in the same run. Precision data: HVA: cv = 2.73%; 5-HIAA: cv = 7.63%; MHPG: cv = 6.89%.

A blood sample (20 ml) for determination of serum concentrations of sex steroids and pituitary hormones was obtained from an antecubital vein immediately before the lumbar puncture. Sex steroids, steroid binding proteins, and pituitary hormones were measured using radioimmunoassays provided by Diagnostic Products, Los Angeles, USA (estradiol, progesterone, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], and prolactin), or Famos Diagnostica, Finland (cortisol binding globulin [CBG], sex hormone binding globulin [SHBG]). All interassay and intraassay variations were less than 10%.

Statistics

CSF concentrations of 5-HIAA, HVA, and MHPG, and the HVA to 5-HIAA ratio, were compared using factorial analysis of variance (ANOVA) with cycle phase (luteal phase and follicular phase, respectively) and group (PMS subjects and controls, respectively) as nominal values. The ANOVA was followed by subsequent t-tests for comparisons of the diagnostic groups split with respect to cycle phase, and for the cycle phases split with respect to diagnosis.

For comparisons between groups, p-values less than .05 were regarded as statistically significant.

Correlation analyses comprised the following parameters: 5-HIAA, HVA, HVA to 5-HIAA ratio, MHPG, estradiol, progesterone, total testosterone, SHBG, CBG, FSH, LH, and prolactin. Two correlation analyses were undertaken; first, the samples were split with respect to menstrual cycle phase, but not with respect to diagnosis; second, the samples were split with respect to menstrual phase as well as to diagnostic group. The correlation analyses were always followed by Fischer's r to z transformation. In order to analyze the differences between groups with respect to a certain correlation, the confidence interval of the r-value was calculated.

RESULTS

CSF Monoamine Metabolite Concentrations

Mean CSF concentrations of 5-HIAA, HVA, and MHPG in the follicular and luteal phases of women with PMS and with controls, respectively, are shown in Figure 1. Factorial ANOVA revealed no significant effect of either cycle phase (MHPG: F = 0.004, p = .9; HVA: F = 0.03, p = .9; 5-HIAA: F = 0.03, p = .9) or the diagnostic group (MHPG: F = 0.8, p = .4; HVA: F = 0.9, p = .3; 5-HIAA: F = 1.7, p = .2) on the concentrations of any of the three monoamine metabolites.

The intraindividual, intersample variations of CSF 5-HIAA, HVA, and MHPG in the subpopulation of individuals from which a CSF sample was obtained both in the follicular phase and the luteal phase are shown in Figure 2A–C. The intraindividual correlations were significantly stronger in the PMS group than in the controls for both HVA (PMS: r = 0.86; controls: r = 0.21; $p < .05$) and 5-HIAA (PMS: r = 0.77; controls: r = −0.44; $p < .001$), but not for MHPG (PMS: r = 0.70; controls: r = 0.24; NS).

The interindividual variation of CSF HVA concentrations was significantly smaller in the follicular phase of the controls, both when compared to the luteal phase of the controls (F = 6.1, $p < .01$) and when compared to the follicular phase of PMS patients (F = 3.7, $p < .05$). With respect to the other metabolites, neither diagnosis nor cycle phase significantly influenced the within-group, interindividual variation.

CSF HVA and CSF 5-HIAA correlated significantly

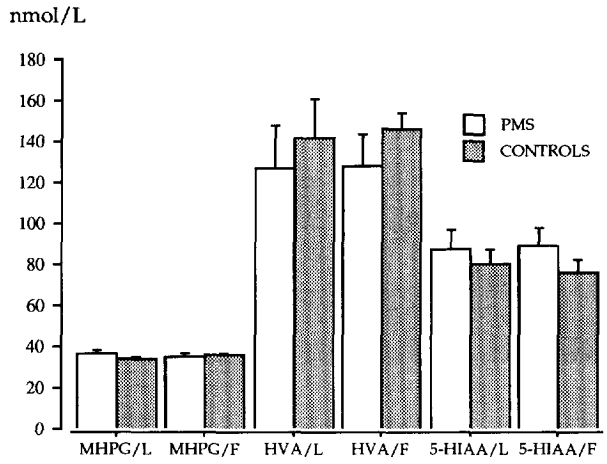


Figure 1. CSF concentrations of MHPG, HVA, and 5-HIAA in the luteal (L) and follicular (F) phases of PMS patients and controls. Bars represent mean ± SEM. n = 9–11. For statistics, see Results.

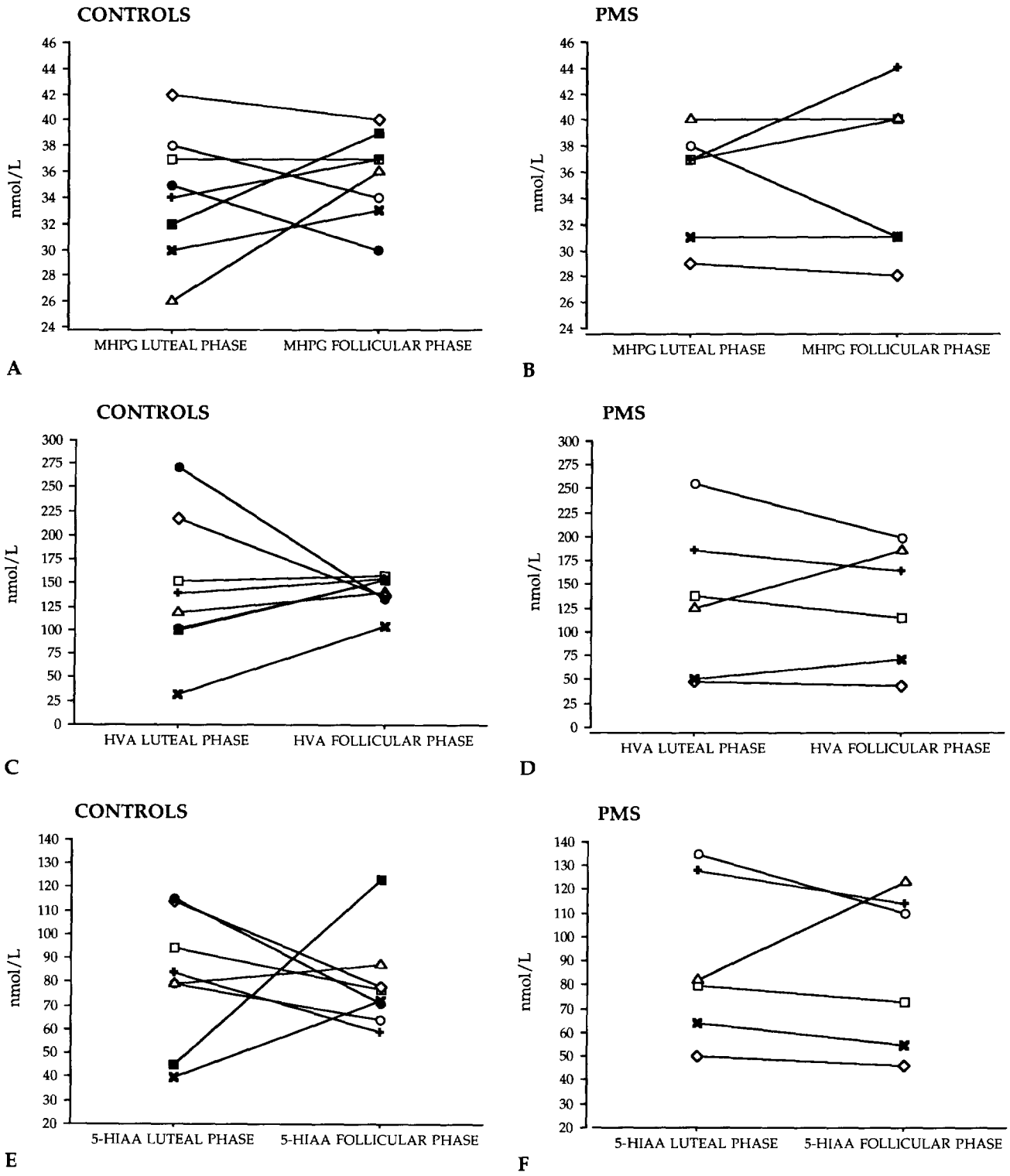


Figure 2. CSF concentrations of MHPG (**A–B**), HVA (**C–D**), and 5-HIAA (**E–F**) in the controls and PMS patients examined in both the luteal phase and the follicular phase. For statistics, see Results.

in the luteal phase of both patients and controls (Figure 3A–B). In contrast, in controls, no correlation between CSF HVA and CSF 5-HIAA was observed in the follicular phase. Also in the PMS group, the HVA versus 5-HIAA correlation appeared weaker in the follicular phase than in the luteal phase; however, the difference in correlation between the follicular and luteal phases, respectively, was statistically significant

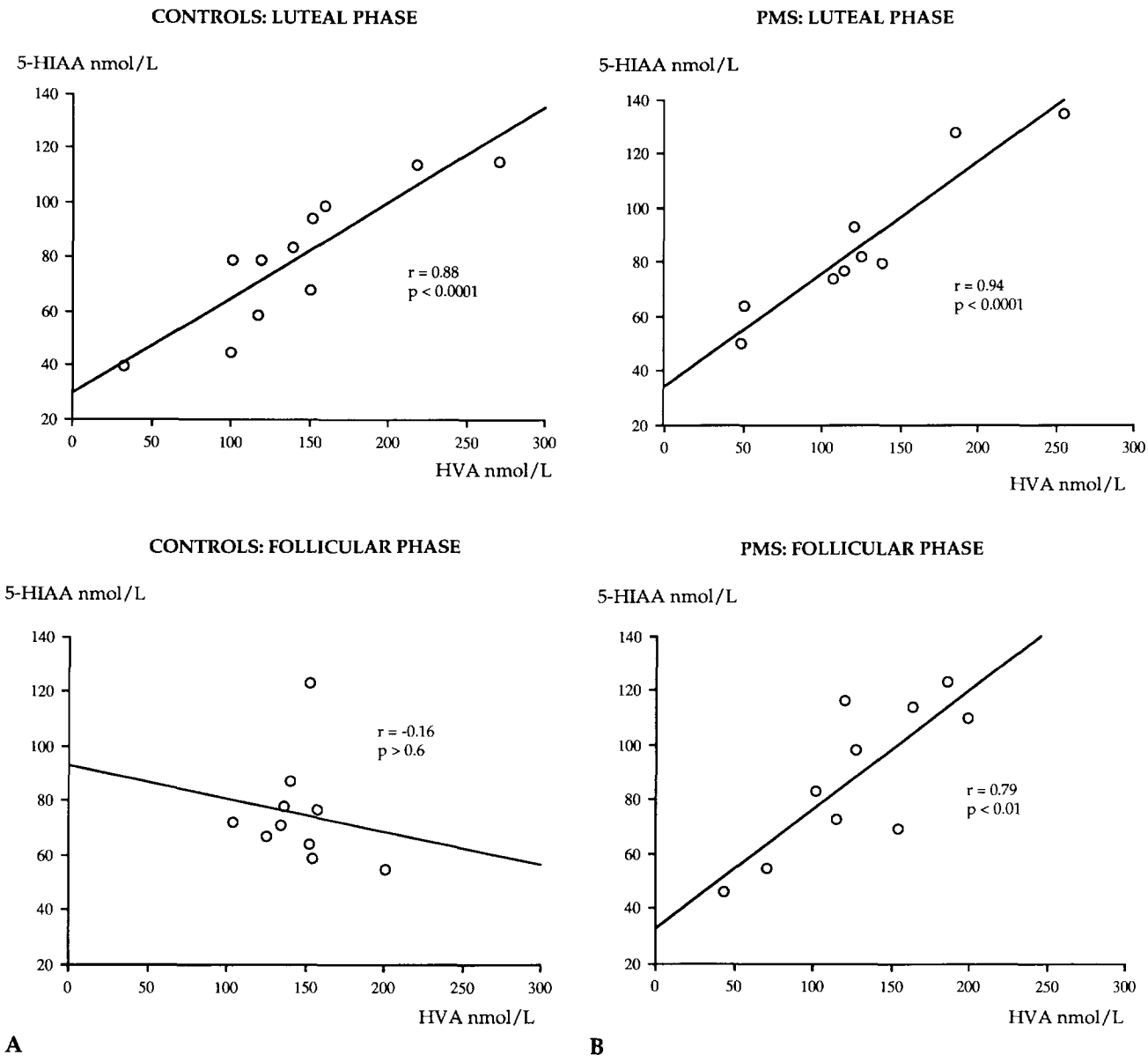


Figure 3. Correlation between CSF 5-HIAA and CSF HVA in the luteal phase and follicular phase of the controls (**A**) and PMS patients (**B**).

($p < .001$) in the controls only. The HVA versus 5-HIAA correlation in the follicular phases was significantly stronger in PMS patients than in controls ($p < .01$).

By means of ANOVA, a significant effect of diagnostic category ($F = 9.4$, $p = .004$), but not of phase ($F = 1.3$, $p = .3$), was observed with respect to the HVA to 5-HIAA ratio. The HVA to 5-HIAA ratio appeared lower in the PMS group both in the follicular phase and the luteal phase (Figure 4); however, the difference was statistically significant in the follicular phase only ($t = 2.8$; $p < .01$). The 5-HIAA to MHPG and HVA to MHPG ratios were not significantly influenced by cycle phase or diagnosis (data not shown).

CSF MHPG correlated weakly to CSF HVA (PMS, luteal phase: $r = 0.46$, $p = .2$; PMS, follicular phase: $r = 0.46$, $p = .2$; controls, luteal phase: $r = 0.44$, $p = .2$; controls, follicular phase $r = 0.66$ $p = .04$) and CSF 5-HIAA (PMS, luteal phase: $r = 0.44$, $p = .3$; PMS, follicular phase: $r = 0.57$, $p = .08$; controls, luteal phase: 0.45, $p = .2$; controls, follicular phase $r = 0.22$, $p = .6$).

Serum Concentrations of Sex Steroids and Pituitary Hormones

Serum levels of estradiol, testosterone, progesterone, FSH, LH, SHBG, and CBG in patients and in controls are presented in Table 1.

Table 1. Serum Concentrations of Pituitary Hormones and Sex Hormones in PMS Patients and in Controls

	Controls	PMS	ANOVA
Estradiol			D: $p = 0.09$
Follicular phase	0.08 ± 0.02	0.32 ± 0.12	Ph: $p = 0.15$
Luteal phase	0.30 ± 0.06	0.30 ± 0.05	D*Ph: $p = 0.09$
Progesterone			D: $p = 0.62$
Follicular phase	1.72 ± 0.26	1.58 ± 0.23	Ph: $p < 0.0001$
Luteal phase	26.21 ± 6.49	22.09 ± 5.37	D*Ph: $p = 0.64$
Testosterone			D: $p = 0.003$
Follicular phase	0.66 ± 0.16	1.14 ± 0.16	Ph: $p = 0.43$
Luteal phase	0.70 ± 0.13	1.39 ± 0.27	D*Ph: $p = 0.56$
SHBG			D: $p = 0.72$
Follicular phase	50.46 ± 5.70	47.73 ± 5.32	Ph: $p = 0.77$
Luteal phase	50.85 ± 3.52	50.14 ± 3.83	D*Ph: $p = 0.83$
CBG			D: $p = 0.09$
Follicular phase	40.48 ± 1.74	38.79 ± 1.95	Ph: $p = 0.93$
Luteal phase	43.22 ± 2.29	36.46 ± 3.54	D*Ph: $p = 0.31$
FSH			D: $p = 0.39$
Follicular phase	1.65 ± 0.11	1.59 ± 0.14	Ph: $p = 0.003$
Luteal phase	1.00 ± 0.18	1.31 ± 0.13	D*Ph: $p = 0.20$
LH			D: $p = 0.44$
Follicular phase	1.24 ± 0.15	1.37 ± 0.29	Ph: $p = 0.38$
Luteal phase	1.01 ± 0.21	1.21 ± 0.22	D*Ph: $p = 0.85$
Prolactin			D: $p = 0.01$
Follicular phase	23.9 ± 5.05	13.01 ± 6.95	Ph: $p = 0.28$
Luteal phase	26.22 ± 3.37	17.94 ± 5.72	D*Ph: $p = 0.77$

Units: estradiol, progesterone, testosterone, SHBG: nmol/L; transcortin: mg/L; prolactin, FSH, LH: μg/L. Abbreviations: D = diagnosis, Ph = cycle phase.

For testosterone, ANOVA revealed a significant influence of diagnostic group (levels being higher in PMS subjects than in controls; $p = .003$), but not of cycle phase. Subsequent 2-tailed *t*-test disclosed significantly higher levels of testosterone in PMS subjects as compared to controls in the luteal phase ($p < .02$) whereas the difference in the follicular phase did not reach statistical significance.

For prolactin, ANOVA revealed a significant influence of diagnostic group (levels being lower in PMS subjects than in controls; $p = .01$), but not of cycle phase. Subsequent 2-tailed *t*-test disclosed significantly lower levels of prolactin in PMS subjects as compared to controls in the follicular phase ($p < .05$) whereas the difference in the luteal phase did not reach statistical significance.

Table 2. Correlations between CSF Monoamine Metabolites and Serum Hormone Concentrations in PMS Patients and in Controls

	All Subjects		PMS		Controls	
	Follicular Phase	Luteal Phase	Follicular Phase	Luteal Phase	Follicular Phase	Luteal Phase
MHPG vs. LH	$r = 0.68$ $p = 0.001$	$r = 0.13$ $p = 0.60$	$r = 0.83$ $p = 0.004$	$r = 0.31$ $p = 0.4$	$r = 0.4$ $p = 0.3$	$r = -0.14$ $p = 0.7$
MHPG vs. test	$r = 0.12$ $p = 0.6$	$r = -0.12$ $p = 0.6$	$r = 0.19$ $p = 0.6$	$r = -0.80$ $p = 0.008$	$r = 0.09$ $p = 0.8$	$r = 0.48$ $p = 0.2$
MHPG vs. estrogen	$r = 0.45$ $p = 0.05$	$r = -0.23$ $p = 0.9$	$r = 0.72$ $p = 0.02$	$r = -0.32$ $p = 0.4$	$r = -0.55$ $p = 0.1$	$r = 0.21$ $p = 0.57$
MHPG vs. prolactin	$r = 0.25$ $p = 0.3$	$r = 0.35$ $p = 0.1$	$r = 0.5$ $p = 0.1$	$r = 0.3$ $p = 0.4$	$r = 0.20$ $p = 0.6$	$r = 0.76$ $p = 0.009$
MHPG vs. SHBG	$r = -0.32$ $p = 0.18$	$r = 0.51$ $p = 0.02$	$r = -0.1$ $p = 1.0$	$r = 0.76$ $p = 0.02$	$r = -0.67$ $p = 0.03$	$r = 0.34$ $p = 0.34$
HVA vs. LH	$r = 0.35$ $p = 0.1$	$r = -0.05$ $p = 0.8$	$r = 0.29$ $p = 0.5$	$r = -0.08$ $p = 0.8$	$r = 0.72$ $p = 0.02$	$r = 0.02$ $p = 1.0$

Shown only are correlations with an *r*-value exceeding 0.7 for at least one cycle phase in at least one of the diagnostic groups.

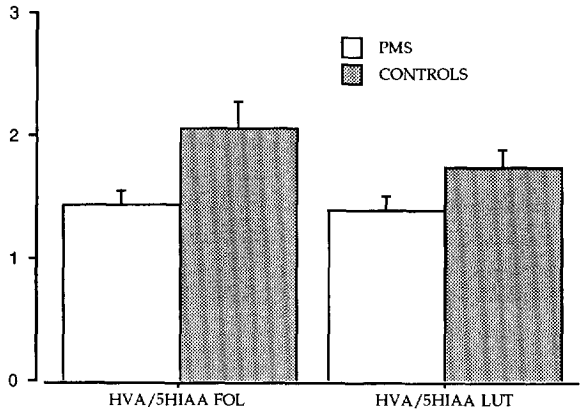


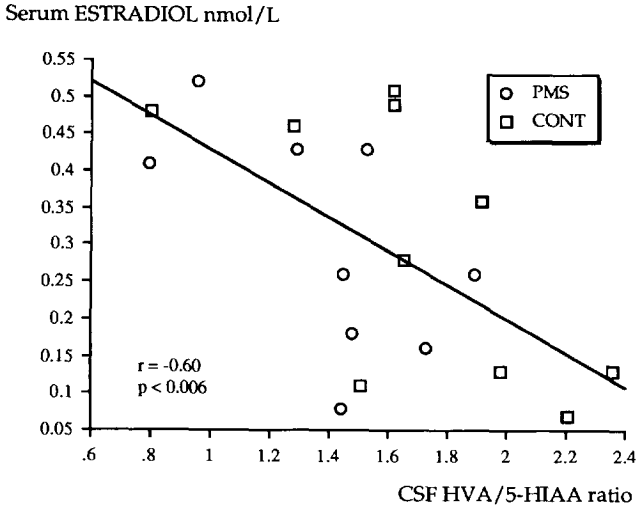
Figure 4. CSF HVA to 5-HIAA ratio in the follicular (FOL) phase and luteal (LUT) phase of PMS patients and controls. For statistics, see Results.

Correlation between CSF Monoamine Metabolites and Hormones

In Table 2 are shown all correlations between CSF monoamine metabolites versus sex steroids and pituitary hormones with r greater than 0.7 in at least one cycle phase, in PMS subjects or in controls.

Given the large number of correlations, analyses undertaken, relations between two factors yielding $r < 0.7$ were regarded as nonsignificant; these data are generally not shown. As an exception, a few correlations not exceeding an r of 0.7, but still regarded as being of possible physiological interest are presented in the text (see the following) and in Figures 5A-C, 6, and 7.

In the luteal phase, but not in the follicular phase, the CSF HVA to 5-HIAA ratio correlated negatively with



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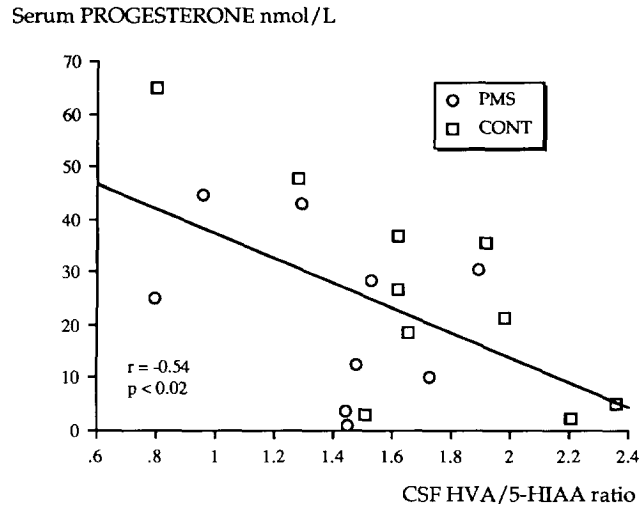

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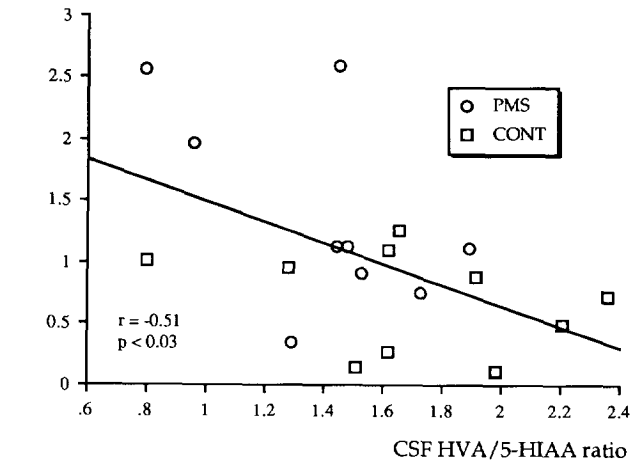

C

Figure 5. Correlation between serum estradiol (**A**), progesterone (**B**), and testosterone (**C**), respectively, and the CSF HVA to 5-HIAA ratio, in the luteal phase of PMS patients and controls.

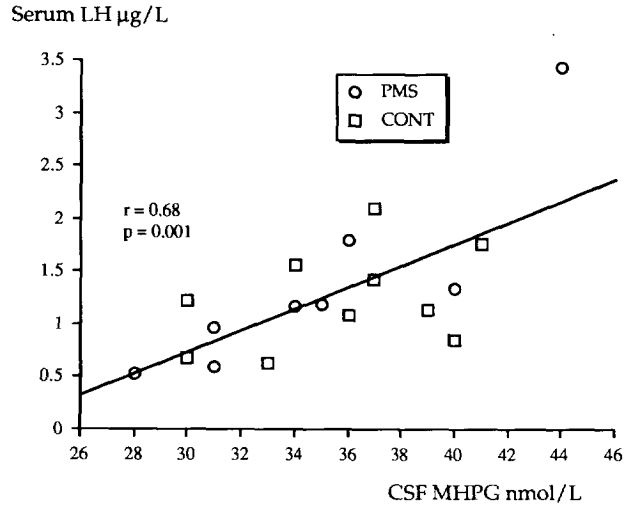

Figure 6. Correlation between serum LH and CSF MHPG concentration in the follicular phase of PMS patients and controls.

serum levels of estradiol, progesterone, and testosterone. In this respect, no significant difference between patients and controls was observed (Figure 5A-C).

In the entire group investigated, serum levels of LH correlated positively with CSF levels of MHPG in the follicular phase, but not in the luteal phase (Table 2, Figure 6).

In the entire group investigated, serum levels of prolactin correlated positively with CSF levels of HVA in the luteal phase, but not in the follicular phase (PMS, luteal phase: $r = 0.68$, $p = .04$; PMS, follicular phase: $r = 0.21$, $p = .6$; controls, luteal phase: $r = 0.52$, $p = .1$; controls, follicular phase: $r = 0.09$, $p = .8$; also see Figure 7).

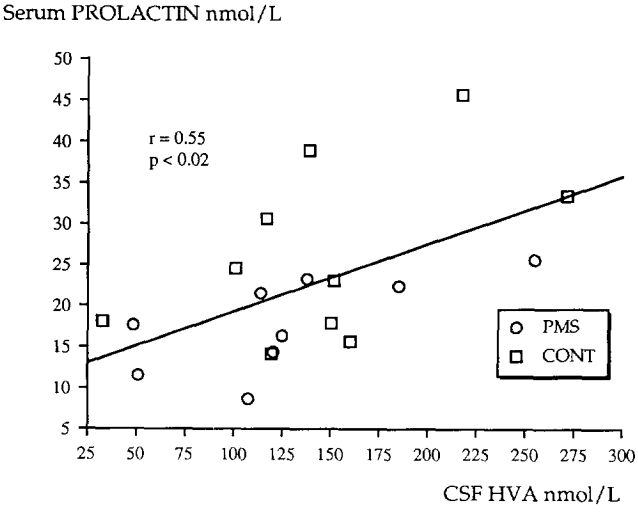

Figure 7. Correlation between serum prolactin and the CSF HVA concentration in the luteal phase of PMS patients and controls.

DISCUSSION

CSF Monoamine Metabolites in Healthy Controls

In the eight women without premenstrual complaints from which CSF samples were obtained both in the luteal phase and in the follicular phase, the intraindividual, intersample variations were found to be considerable for all three monoamine metabolites; in contrast, mean CSF metabolite concentrations in the follicular phase did not differ from those in the luteal phase.

Previous data on the intraindividual stability of CSF monoamine metabolites are sparse. Hildebrand and coworkers (1990), taking repeated samples from hospitalized patients with cognitive disorder, showed substantial intraindividual variations, but showed very small differences in group means with respect to CSF HVA, MHPG, and 5-HIAA. In a study by Träskman-Bendz and coworkers (1984), the variability in CSF samples obtained from healthy volunteers (male and female), with an interval of 2 weeks to 8 weeks, was relatively modest, with the correlations between the first value and the second value being stronger for all three metabolites than the correlations observed in the present study. The latter finding suggests that the large variability in CSF metabolite concentrations in controls observed in the present study may be because the samples were taken at different phases of the menstrual cycle rather than randomly with respect to cycle phase. Interestingly, in the study by Träskman-Bendz and coworkers (1984), larger intraindividual variations in CSF levels of 5-HIAA and HVA were found in females than in males.

Although the mean concentration of HVA in CSF were similar in the luteal and follicular phases, in normal controls the interindividual variation was considerably smaller in the follicular phase than in the luteal phase. Moreover, whereas in the luteal phase, the CSF concentrations of HVA and 5-HIAA strongly correlated, in the follicular phase, no such correlation was observed. This latter finding contrasts sharply to the large body of previous data showing a significant correlation between the serotonin and dopamine metabolites in various populations regardless of age, sex, and psychiatric diagnosis (Ågren et al. 1986). However, albeit CSF concentrations of HVA and 5-HIAA have previously been frequently studied in women of fertile age, this is, to our knowledge, the first report on CSF monoamine concentrations obtained in the follicular phase before the midcycle rise in serum estradiol and progesterone. Hence, the lack of correlation between HVA and 5-HIAA in the early follicular phase is neither supported nor contradicted by earlier studies.

The possible differences in HVA variability, and in HVA vs 5-HIAA correlation, between samples obtained from the follicular and luteal phases, respectively, in-

dicates that sex steroids may influence the dopamine activity and/or metabolism (cf. Di Paolo et al. 1989) as well as the interplay between dopamine and serotonin. Further support for this concept was obtained by the negative correlations between sex steroids and the HVA to 5-HIAA ratio observed in the luteal phase of the entire population (vide infra). Notably, in a study by Koslow and coworkers (1983), the HVA vs 5-HIAA correlation was stronger in female than in male healthy controls.

Due to the small number of subjects included in this study, the possibility that the small HVA variability, as well as the lack of HVA to 5-HIAA correlation, in the follicular phase of controls is accidental, should not be ignored.

CSF Monoamine Metabolites in Women with PMS

No difference was observed when PMS subjects and controls were compared with respect to mean concentrations of CSF 5-HIAA, HVA, and MHPG; moreover, like controls, women with PMS displayed no cycle related changes in mean CSF monoamine metabolite concentrations. The finding that CSF HVA and 5-HIAA levels in women with PMS are similar in the luteal and follicular phases is in agreement with a previous report from Parry and coworkers (1991). Our finding that MHPG levels are similar in the luteal and follicular phases is, however, in contrast with the study by Parry and coworkers which showed increased MHPG levels in the luteal phase in women with PMS.

In previous literature, a relation between low CSF 5-HIAA levels and proneness to respond to serotonin reuptake inhibitors have been suggested (Åsberg et al., 1986a). However, given the dramatic therapeutic effect of serotonin reuptake inhibitors in the treatment of PMS (Eriksson et al. 1990; Rickels et al. 1990; Stone et al. 1991; Menkes et al. 1992; Sunblad et al. 1992; Wood et al. 1992; Sunblad et al. 1993), the present finding that CSF 5-HIAA levels appear normal in a group of women with PMS, when compared to controls with no premenstrual complaints, underlines that a low CSF level of 5-HIAA is not a characteristic feature of all conditions responding to antidepressants with a serotonergic profile. Similarly, previous studies have shown that CSF concentrations of 5-HIAA are not decreased in patients with panic disorder (Eriksson et al. 1992) or obsessive compulsive disorder (Thorén et al. 1980; Insel et al. 1985) in spite of the fact that these conditions also respond favorably to serotonin reuptake inhibitors (Eriksson and Humble 1990).

The finding that CSF 5-HIAA levels are not lower in PMS subjects as compared to controls, and also not lower in the luteal phase as compared to the follicular phase, does not exclude the possibility that PMS is associated with a sex steroid induced change in serotonin turnover in a restricted region of the brain not reflected by the CSF 5-HIAA concentration. Also, the possibility that PMS may be associated with a change in serotonin receptor responsiveness—rather than in serotonin metabolism—should not be ignored (cf Yatham et al. 1989). Several earlier studies do lend support for the concept that premenstrual changes in mood are indeed associated with measurable changes in various aspects of serotonergic function in the brain and in the periphery (Taylor et al. 1984; Ashby et al. 1988; Bancroft et al. 1991; Rojansky et al. 1991).

Although mean concentrations of CSF monoamine metabolites did not separate patients from controls, the intraindividual variability, when comparing samples from the follicular phase and the luteal phase, respectively, was significantly lower in PMS subjects than in controls for both HVA and 5-HIAA. As in the controls, the correlation between HVA and 5-HIAA appeared weaker in the follicular phase as compared to the luteal phase also in women with PMS; however, the HVA vs 5-HIAA correlation in the follicular phase was significantly higher in PMS subjects than in the controls, and the difference between the two phases with respect to HVA vs 5-HIAA correlation reached statistical significance in the controls only. Thus, with respect to individual HVA and 5-HIAA levels, as well as the HVA vs 5-HIAA correlation, PMS patients appeared *less* influenced by cycle phase than did the controls. When interpreting this apparent difference between patients and the controls, it should be taken into consideration that the serum concentrations of estradiol in the follicular phase tended to be higher in women with PMS than in the controls ($p = .06$); thus, information regarding CSF monoamine concentrations in a situation with very low (<0.1 nmol/L) serum levels of estradiol was obtained from the controls only.

Several recent papers have emphasized the possible importance of the HVA to 5-HIAA ratio as an index of serotonin/dopamine interactions and as a marker of psychiatric morbidity (Ågren et al., 1986; Roy et al., 1986; Risby et al. 1987; Ågren et al. 1988; Hsiao et al. 1993; Potter and Manji, 1993). Interestingly, in depression, a reduced HVA to 5-HIAA ratio appears to be a more robust biological marker than the actual concentrations of HVA and 5-HIAA, respectively (Roy et al. 1986; Reddy et al. 1992). Hence, the present finding that the HVA to 5-HIAA ratio may be lower in women with PMS than in the controls suggests that PMS and depression may have pathophysiological mechanisms in common; needless to say, the efficacy of serotonin reuptake inhibitors in the treatment of PMS (for references, see previous) lends further support for this concept.

Pituitary and Sex Hormones in PMS Patients and Controls

A comparison of PMS patients and controls with respect to serum hormonal levels was not the primary

scope of this paper; thus, hormonal levels in a larger group, of which the women exposed to lumbar puncture constitute a subpopulation, will be presented elsewhere. However, it should be noted that serum levels of total testosterone were significantly higher in women with PMS as compared to controls; this finding is in line with our previously reported observation, based on data from different groups of PMS patients and controls, showing significantly higher levels of free testosterone in women with PMS (Eriksson et al. 1992). Also noteworthy is our finding that serum levels of prolactin were significantly lower in the follicular phase of PMS subjects (cf Andersch et al. 1979).

Influence of Sex Steroids on the HVA to 5-HIAA Ratio

When all subjects—patients and controls—were analyzed together, the HVA vs 5-HIAA correlation turned out to be considerably stronger in the luteal phase, when serum levels of sex steroids are high, than in the follicular phase, when estradiol and progesterone are low ($p < .01$); hence, it may be suggested that the interaction between HVA and 5-HIAA in women could be under the influence of steroid hormones. In support for this assumption, in the luteal phase the HVA to 5-HIAA ratio (but neither the HVA nor the 5-HIAA concentration *per se*) correlated negatively with estradiol, progesterone, and total testosterone.

The mechanisms underlying the strong correlation between CSF HVA and 5-HIAA usually observed in man is obscure (for discussion, see Ågren et al. 1986; Hsiao et al. 1993), and so is the possible influence of sex steroids on this interaction. According to one hypothesis, CSF 5-HIAA concentrations is a reflection of the monoamine oxidase (MAO) activity rather than of serotonin synthesis or release (Wolf et al. 1985). Because in man both serotonin and dopamine are metabolized by MAO A and MAO B, the possibility that a change in MAO activity may change the relation between 5-HIAA and HVA in CSF should not be ignored. In this context, the well established influence of estradiol, testosterone, and progesterone on brain MAO A and MAO B activity (Luine et al. 1975; Leung et al. 1980; Chevillard et al. 1981; Vaccari and Biassoni 1982; Luine and Rhodes 1983) is worth recalling; however, the physiological significance of this steroid influence on MAO activity still remains to be established. Moreover, animal experiments have revealed multiple examples of interactions between serotonin and dopamine not related to MAO activity (e.g. Ågren et al. 1986; Benloucif and Galloway 1991; Nissbrandt et al. 1992); likewise, sex steroids have been shown to influence both dopamine and serotonin activity by a number of various mechanisms (Engel et al. 1979; Sietniks et al. 1983; Long et al. 1983; Battaner et al. 1987; Bitar et al. 1991). Obviously, further studies are warranted in order to clarify the possible relations between sex steroids and the CSF HVA to 5-HIAA ratio.

Relation between Pituitary Hormones and CSF Monoamine Metabolites

Because a large number of correlation analyses were undertaken when evaluating the possible interplay between CSF monoamine metabolites on the one hand and gonadal and pituitary hormones on the other, correlations of weak significance and without obvious physiological significance should be interpreted with caution; however, we observed two examples of an apparent covariance between a pituitary hormone and a CSF monoamine metabolite that deserves attention.

First, in the follicular phase, serum levels of LH correlated strongly to CSF levels of the noradrenaline metabolite, MHPG. Earlier animal studies have shown noradrenaline to be a major regulator of GnRH/LH release; thus, the progesterone induced midcycle LH surge appears to be noradrenaline mediated (see Adler et al. 1983). When interpreting the observed correlation between LH and MHPG, both central and peripheral mechanisms should be considered. Thus, it has been suggested that CSF MHPG partly emanates from peripheral sources (Kopin et al. 1983); moreover, several studies have shown that the midcycle LH surge is accompanied by an increase in serum levels of noradrenaline (Badano et al. 1978; also see Nagle and Rosner 1980). Interestingly, in a recent study in women with polycystic ovary syndrome, plasma MHPG levels were shown to correlate with the magnitude of the LH response to LHRH, indicating that noradrenaline influences the responsiveness of the pituitary to the LH releasing hormone (Yoshino et al. 1992).

Second, in the luteal phase, but not in the follicular phase, serum levels of prolactin correlated positively with CSF levels of HVA. Whereas tuberoinfundibular dopamine neurons inhibits prolactin release, prolactin has been shown to stimulate dopamine activity in the hypothalamus (Hökfelt and Fuxe 1972), and, perhaps, also in the striatum (Bédard et al. 1984). Further studies are warranted to establish whether the observed correlation between CSF HVA and serum prolactin is a reflection of the physiological interplay between dopamine and prolactin, or merely accidental.

CONCLUSION

In a small group of healthy women without premenstrual complaints, the interindividual variability in CSF HVA levels appeared smaller, and the HVA vs 5-HIAA correlation weaker, in the follicular phase than in the luteal phase; in contrast, the menstrual cycle phase did not influence the mean concentrations of CSF mono-

amine metabolites. In PMS patients, the intraindividual variability of CSF metabolites seemed smaller than in controls; moreover, in the follicular phase, the interindividual HVA variability appeared greater, the HVA vs 5-HIAA correlation stronger, and the HVA to 5-HIAA ratio lower than in controls. In the entire group of subjects investigated, the CSF HVA to 5-HIAA ratio correlated negatively with serum levels of estradiol, progesterone, and testosterone in the follicular phase. Albeit these findings were obtained from small groups of subjects and hence should be interpreted with great caution, they may encourage further studies on the possible influence of sex steroids on CSF concentrations of HVA and 5-HIAA and on the relation between these two metabolites. When CSF samples are obtained for determination of monoamine metabolites from women of fertile age, the menstrual cycle phase at the time of sampling is a factor of a putative importance that should not be ignored.

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