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SERUM GONADAL STEROID HORMONES IN YOUNG SCHIZOPHRENIC PATIENTS

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SUMMARY

Psychosis is reported to show a later age of onset in women than in men and its nature and course in women may also differ. The purpose of this study was to determine if levels of four steroid hormones at the start of early onset psychosis differ from the levels of other groups of young people and if predicted low levels of estrogen (E2) are a feature of female psychosis. Two blood samples from 22 young psychotic patients were analysed by radioimmunoassay for E2, progesterone (PROG), testosterone (TE), and dehydroepiandrosterone sulphate (DHEAS). Female psychotic patients showed E2 levels lower than matched healthy cycling controls but higher than those on a contraceptive pill; they also showed higher TE levels than controls. Male psychotic patients had higher DHEAS levels than healthy or obsessive compulsive disorder (OCD) subjects. We suggest that illness-related changes of steroids can be measured superimposed on medication-induced changes and that lower E2 levels in psychotic women may increase their vulnerability to psychosis. Changes of TE in female and DHEAS in male psychotics may be more a consequence of the illness.

Keywords—Schizophrenia; Gender; Adolescent; Obsessive compulsive disorder (OCD); Estrogen; Progesterone; Testosterone; Dehydroepiandrosterone sulphate (DHEAS).

INTRODUCTION

IN A SAMPLE of 625 male and 449 female schizophrenics, Kraepelin (1909–1915) noted that the first episode started later in females. This observation was repeated many times in the next few decades (Hartmann & Meyer, 1969; Pollock, 1926; Strömgren, 1935). Recent studies show that the mean onset for females peaks 1.5–5 years after that for males, with a subsequent peak around the menopause (Angermeyer & Kuhn 1988; Häfner et al., 1989; Lewine et al., 1981).

The possibility of a later onset of psychosis in women raises two questions. First, is female psychosis a separate entity from male psychosis? There are reports that psychotic women show an increased prevalence of hallucinations (Rector & Seeman, 1992) and a better course (Zubin et al., 1985). Second, could an aspect of female physiology such as the secretion of gonadal steroids delay onset and perhaps characterize female psychosis?

What evidence is relevant to this second question? Pregnancy, associated with high

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levels of gonadal steroids, appears to protect against relapse (Chang & Renshaw, 1986). But where abrupt changes of circulating gonadal steroids occur (e.g., childbirth and menopause), there is an increased risk of psychosis (McNeil, 1987; Kendell et al., 1987). Admissions can peak in the perimenstrual period (Riecher–Rössler & Häfner, 1993). Further implication of gonadal steroid levels in the expression of psychosis may be found in reports of increased menstrual disorders in psychotic women before the era when neuroleptic treatment could cause interference (Hanse, 1923; Ripley & Papanicolaou, 1942).

Two bodies of literature support the proposal that E2 may protect against psychosis. First, 40 years' clinical experience shows that dopamine antagonists reduce the experience and expression of psychotic symptoms and relapse (Straube & Oades, 1992). Second, many laboratory studies show that E2 can modulate dopamine activity, binding and behavior in a way that parallels that of neuroleptics (Becker, 1990; Di Paolo et al., 1984). The relevance of these results to the human condition is supported by the increased prevalence of neuroleptic-induced tardive dyskinesia in women, particularly after the menopause (Crane, 1968; Kane & Smith, 1982). PROG, too, can modulate dopamine activity (Dluzen & Ramirez, 1987, 1991). Further there is a large literature on the influence of E2, TE (Oades, 1979), and the catecholamines on attention-related processes (Oades, 1985), which are among those functions most clearly affected by psychosis.

Could different levels of circulating E2 in females (or as a metabolite of TE in males) contribute to the precipitation of psychosis or protection from events triggering it? The potential for neuroleptics to interfere in steroid secretion (Beumont & Bergen, 1982) has inhibited the study of these hormones in psychotic women on neuroleptic treatment. This is unfortunate, for despite identification of the mechanism, namely the disruption of the positive feedback action of E2 on pituitary gonadotropin release (Le Gros et al., 1975), the consequences in terms of the type of neuroleptic and its dose on steroid hormones has not received as much attention as, for example, the effects on prolactin. Rather the emphasis has been on the undoubted association of the increased incidence of menstrual dysfunction with neuroleptic treatment. In this context we were encouraged to pursue the study of steroid levels in neuroleptic-treated patients, taking note of the following three points: 1) hypogonadal-induced menstrual dysfunction is usually associated with low E2 but high prolactin production; 2) normal levels of gonadotropin, luteinizing hormone and TE have been recorded before and after neuroleptic treatment (Rinieris et al., 1989; Siris et al., 1980); and 3) the expression of symptoms in psychotic women may correlate negatively with E2 levels even in the absence of any correlation with medication in terms of chlorpromazine equivalents (Riecher–Rössler et al., 1992).

There are several ways in which E2 (or other steroids) may affect psychosis. Low E2 levels may 1) increase vulnerability to factors that trigger psychosis, or 2) facilitate the expression of symptoms in psychosis. While measures of E2 from psychotics may be affected by neuroleptics, if the vulnerability role is more pertinent, then low E2 levels should be *relatively insensitive to neuroleptic dose*. This question can be approached by studying those at risk for schizophrenia or young acutely psychotic patients in their first episode.

We present preliminary data relevant to the postulated role of E2 in vulnerability. We hypothesized that *young* psychotic women would show low levels of circulating E2 compared to healthy age-matched subjects independent of the type or amount of neuroleptic administered. In contrast, PROG levels may depend on levels of medication.

An alternative explanation of gender differences in psychosis onset may lie with

changed androgen levels in males. This has received sparse attention to date (review Oades, 1982). Small decreases (Beumont et al., 1974) or increases of TE (Mason et al., 1988) and of circadian changes of DHEAS have been reported in male schizophrenics (Tourney & Erb, 1979). We would predict that *young* psychotic males, who would have less circulating E2 than females, would not show low E2 levels compared with healthy males. One reason for this prediction is that animal studies report that male neostriatum is less sensitive to the dopamine effects of E2 (Becker, 1990). But as an adolescent onset of psychosis is often associated with a poor outcome, the possibility that a change of androgen metabolism is related to early onset in psychotic men remains. However, the extant literature does not allow a satisfactory prediction for the nature of a change.

METHODS

Subjects

There were 11 male and 11 female inpatients with schizophrenia-spectrum psychoses (SCH-M and SCH-F). There were two male control groups [13 healthy subjects (CON-M) and 7 inpatients with obsessive compulsive disorder (OCD)] and two female control groups [10 healthy subjects with regular menstrual cycles (CON-F) and 9 taking a low dose combined contraceptive pill (PIL)]. Clinical data are shown in Tables I, II, and IV.

DSM-IIIR diagnoses were made by a clinical psychiatrist and confirmed by four persons who rated a videotape of a semi-structured clinical interview. The duration requirement for a diagnosis of schizophrenia was not initially adhered to, but was satisfied soon afterwards in all cases. All subjects consented to participate after being informed on the nature and content of the research and the parents of those under 18 years gave signed consent.

All subjects younger than 18 years were postmenarchical and assessed for somatic (wrist X-ray) and sexual development (Tanner scale; a 6-point assessment of secondery sexual features where half points reflect means of differing pubic and breast ratings, Marshall & Tanner, 1986). SCH and CON subjects were matched individually within 0.5 points for sexual maturity if under Tanner level 5 and for age/bone-age within 1.5 years. Data for the youngest control were lost. Separate reference is made in the discussion to two premenarchical subjects and two older SCH patients whose data were not included in the statistical analyses.

Males were well matched for years of education (SCH-M 11.2, SD 2.5; CON-M 10.9, SD 2.1; OCD 10.5, SD 2.0); but there was a significant difference for females (SCH-F 10.2, SD 2.8; CON-F 13.9, SD 3.1; $t = +2.88$ $p = .01$). All subjects were screened to exclude a history of organic disorder or substance abuse. Controls reported that they were free of present and past psychiatric disturbance and of medication. Neuroleptic medication is expressed in chlorpromazine (CPZ) equivalents (Rey et al., 1989) and anticholinergic medication in mg/day biperidene. The therapist rated symptom severity with the Brief Psychiatric Rating Scale (BPRS) for SCH or the Yale-Brown Scale (YBOCS) for OCD patients.

Blood Samples and Analysis

One blood sample from each control and two from each psychotic patient, separated by 1–3 weeks (during which a cognitive test battery was performed), were taken between 0815 and 0845, centrifuged and frozen (−20°C) prior to analysis blind to diagnosis.

TABLE I. PATIENT CLINICAL DATA AND BACKGROUND

	DSM-IIIR diagnosis (axis 1) 295.						CPZ	anti	BPRS/YBOCS
	.1	.2	.3	.4	.7	.9	equiv	ACh	sum
SCH-F	—	1	4	1	4	1	781 (666)*	1.8 (2.8)†	49 (18)
SCH-M	2	—	5	3	1		1347 (894)*	4.2 (2.1)†	60 (13)
OCD-M			300.3				No medication		20 (6)

Mean	Current episode§ (admission) (1st, 2nd, etc)	Length episode (months)	Duration symptoms (years)	Perinatal problems¶	Family pathology#
SCH-F	2.4‡ (1.9)	3.4 (3.8)	3.4‡ (3.5)	0.4 (0.7)	0.5 (0.7)
CON-F	0	0	0	0.4 (0.7)	0.3 (0.7)
PIL	0	0	0	0.2 (0.4)	0.1 (0.3)
SCH-M	2.1 (1.6)	1.9 (1.2)	2.6 (2.6)	1.1 (0.9)	0.9 (0.8)
OCD	1.0 (0)	2.7 (1.6)	2.4 (2.1)	0.7 (0.9)	0.6 (0.8)
CON-M	0	0	0	0.8 (0.8)	0.3 (0.6)

SDs are in parentheses.

* CPZ equivalents: SCH-F range 0–2100 [neuroleptic (n), clozapine (5), haloperidol (4), fluspirilene (1), 0 (1)]; SCH-M range 120–3000 [neuroleptic (n), clozapine (1), haloperidol (6), fluphenazine (2), perazine (1), 0 (1)].

† Biperidene: SCH-F range 0 (n = 7) to 8, SCH-M 0 (n = 1) to 8 mg/day.

‡ Episode: for n = 9 <25 years of age, episode 2.1 (SD 1.8), symptom onset 2.5 (SD 3.0) years ago.

§ Number of episodes (inc. current one) followed by duration since admission, followed by duration since first clinical symptom (family interview at admission).

¶ Perinatal problems rated in three categories—absent (0), minor (1), or major (2) (Schwarzkopf et al., 1989; Straube & Oades, 1992).

First degree relatives without psychiatric diagnosis = 0; non-psychotic/non-OCD diagnoses in SCH/OCD patients' family = 1, or diagnoses of psychosis/OCD in SCH or OCD patients' family = 2.

17-B-estradiol (E2), PROG, DHEAS, and total unconjugated TE were estimated by radioimmunoassay (^{125}I) kits provided by Sorin Biomedica, Germany. Similarly, luteinizing hormone (LH) and follicular-stimulating hormone (FSH) were measured by Kodak Diagnostics with 2nd IRP-HMG standards. Intra- and inter-assay variations were <5% and 10%, respectively.

We report absolute hormone values for males and for TE and DHEAS in females, but standardized values for postmenarchical female E2 and PROG. Standardized values were obtained in two stages. First, we estimated the time of the cycle when the sample was taken from a) patient information; b) ward records; and c) LH and FSH measures. While patient information is known to be unreliable, youth-ward personnel were usually aware of the timing of menses in teenagers. Cycle length was recorded as a percentage to adjust for unusual duration. Second, we projected both patient and control data on standard curves obtained for normal women (Ross et al., 1970 and calculated the ratio of experimental to norm values. In two cases where the menses was missed, a third sample was taken.

TABLE II. HORMONE LEVELS IN FEMALE SUBJECT GROUPS

	Age	Bone age	Tanner level	Weight (kg)	E2 (standardized units)	PROG	TE (ng/ml)	DHEAS (μg/ml)
SCH-F $n = 11$	18.4 (4.1)	18.4 (3.8)	4.50 (0.9)	58 (9)	0.35*† (0.18)	4.51 (4.45)	0.71*‡ (0.34)	2.51 (1.29)
Range	11.4–24.4§	13.5–24.0§	2.5–6.0	46–77				
CON-F $n = 10$	20.3 (3.2)	20.2 (2.9)	4.85 (.67)	60 (6)	0.68 (0.17)	3.82 (4.28)	0.41 (0.11)	2.81 (1.55)
Range	14.4–23.3	15.0–23.0	3.0–5.5	50–68				
PIL $n = 9$	22.3 (2.1)	22.2 (2.1)	5.06 (.17)	58 (11)	0.10 (0.08)	1.42 (1.29)	0.18 (0.16)	1.40 (0.64)
Range	21.5–24.0	21.5–24.0	5.0–5.5	47–76				

SDs are in parentheses.

* MANOVA $F(8,48) = 10.31$, $p < .0001$; MANCOVA $F(8,40) = 8.24$ $p < .0001$;
E2: $F(2,25) = 33.8$, $p < .0001$ (SCH < CON, SCH > PIL, CON > PIL Scheffe $p < .01$);
PROG: $F(2,25) = 2.0$, $p > .2$; TE: $F(2,25) = 4.5$, $p < .03$ (SCH > CON, SCH > PIL Scheffe $p < .02$; CON > PIL $p = 0.057$); DHEAS: $F(2,25) = 2.9$, $p > .07$.

† E2 for four paranoid vs. seven nonparanoid diagnoses, 0.29 vs. 0.35;

‡ Te for four paranoid vs. seven nonparanoid diagnoses, 0.65 vs. 0.72.

§ These data do not include two premenarchical subjects and two older subjects aged 29.7 and 31.1 years referred to separately in the text.

Separate multivariate analyses of variance and covariance was performed for both sexes (three groups and four hormone measures each) followed by one-way ANOVA and post-hoc Scheffe tests. Covariates studied included four measures of development (age, bone-age, Tanner-rating, and weight) and medication (CPZ equivalents). Age measures proved redundant and chronological age was dropped from the reported analyses. Dependent measure *t*-tests were performed on succesive samples and independent measure *t*-tests on other subject variables. Pearson correlation coefficients were calculated prior to separate linear and stepwise multiple regression analyses of the contribution of developmental (Tanner, bone-age, and weight), medication and symptom-severity to the variance of the hormone measures. Two-tailed probabilities are given.

RESULTS

Female Subjects

Early vs. late-cycle measures. There were no significant differences between female groups on age and development measures (age SDs for SCH and CON and Tanner SDs for CON and PIL were equivalent: see Table II). There were no significant differences between the first and second samples from SCH-F for E2 (0.35 SD 0.17 vs. 0.35 SD 0.18), TE (0.71 SD 0.37 vs. 0.70 SD 0.33), and DHEAS (2.37 SD 1.10 vs. 2.66 SD 1.55). Comparisons of measures taken in the first and second halves of the menstrual cycle in SCH-F showed no significant differences for E2 (t −0.77, $p = .46$), TE (t −0.17, $p = .87$) and DHEAS (t +0.85, $p = .41$). There were no marked differences in samples taken from CON-F in the early ($n = 6$) and late cycle phases ($n = 4$).

PROG levels did differ between first and second samples in SCH-F (6.18 SD 7.35 vs. 2.73 SD 2.39), largely reflecting early and late cycle measures (6.52 SD 7.15 vs. 1.14 SD 2.41). But this coincided with similar early/late cycle changes recorded in CON-F (5.61 SD 4.84 vs. 1.14 SD 0.10) and thus probably reflects a methodological factor *consistent*

between groups (e.g., differences in the timing of the PROG fall at the end of the cycle between the adult reference and our young population). There were no between-group differences on early (t 0.28, p .78) and late-cycle measures (t 1.02, p = .33).

Covariance analysis. A comparison of the measures of E2, PROG, TE, and DHEAS for the three groups of female subjects (Table II) clearly show: 1) E2 levels in SCH-F were low with respect to CON-F but high with respect to PIL; 2) high levels of TE in SCH-F with respect to both healthy groups; and 3) no differences between groups on measures of PROG and DHEAS.

Correlational analysis. Across groups body weights (within percentile range 3–97) correlated weakly with other development measures (r = 0.2–0.3 p > .12) and not with hormone measures, medication or BPRS ratings (r = +0.2 to −0.1, Table III). Within groups developmental measures intercorrelated, but there was no relationship to E2 (r = −0.17 to +0.14). E2 was unrelated to medication or illness severity (r = −0.18 to −0.23).

TE measures tended to be related to developmental variables in healthy but not in SCH-F subjects (e.g., age r = −0.6 vs. +0.14). Illness severity rather than medication was positively associated with TE levels (r = +0.7 p < .04 vs. +0.28). Tanner-ratings also correlated with BPRS scores (r = +0.67, p < .04). DHEAS measures correlated with Tanner-ratings and PROG measures, r = +0.6–0.7, p < .05.

Regression analysis. Analysis with E2 as dependent variable showed that Tanner-rating, weight and bone-age accounted for 2% of the variance for all subjects. Of interest is the contrast of the SCH-F group, where bone-age and weight contributed 3–16% to

TABLE III. HORMONE CORRELATIONS

	Age*	Bone age	Tanner level	Weight (kg)	PROG	TE	DHEAS	BPRS	CPZ
E2									
SCH-F	.13	.14	−.17	−.04	.22	−.07	−.02	−.23	−.18
CON-F	.38	.41	.37	.44	−.26	−.04	−.28		
PIL	.14	.14	−.15	−.29	.47	−.22	.90¶		
TE									
SCH-F	.14	.11	.48	.20	.17		.29	.66†	.28
CON-F	−.59	−.60	.02	.70‡	.17		.63		
PIL	−.59	−.56	.81§	−.29	.38		−.26		
	Age#	**Bone age**	**Tanner level**	**Weight (kg)**	**E2**	**TE**	**PROG**	**BPRS**	**CPZ**
DHEAS									
SCH-M	.46	.45	.42	.05	.24	.09	−.47	−.22	.15
CON-M	.38	.32	.59†	.12	.58†	.42	−.04		
OCD	.44	.42	.49	.15	.68	.64	−.18		

*Correlations for age, bone-age, Tanner, and weight n = 30, r = +0.67–+0.99, p < .001;
#Correlations for age, bone-age, Tanner, and weight n = 31, r = +0.51–+0.96, p < .005 (wt. r = +.46, p < .01).
†p < .04; ‡ p < .025; § p < .008; ¶ p < .001;
The Bonferroni procedure cautions setting alpha at 0.005.

the variance in E2 levels accounted for by the developmental measures ($p > .3$), with the CON-F group where these developmental measures made up 60–69% of the variance ($p < .04$). Separate step-wise analysis of medication and BPRS ratings in the SCH-F group showed contributions of 6% and 3% respectively ($p = .73$).

Analysis for all groups with TE as dependent variable showed that the measures of age, bone-age, and Tanner-ratings made a nonsignificant 7% contribution to the variance in TE levels. Comparison of SCH-F with CON-F groups showed an important difference of emphasis between the groups. Thus developmental measures made up 49.2% of the TE variance in SCH-F (Tanner-ratings 24%, $p = .13$ and weight 12%). In contrast in the CON-F group developmental measures accounted for 61% of the TE variance (weight 49%, $p = .025$; Tanner-ratings 5%). Medication and BPRS measures of severity explained 70% of the variance in the SCH-F group. Both contributed significantly (CPZ 49%, BPRS 21%, $p < 0.05$) sharing 22% of the variance.

In view of the small number of subjects in these analyses we caution against too close an interpretation of the precise values. However, outlying data did not play a determining role [e.g., for medication and E2, Mahalonobis values, measures of the distance of a case from the average of the variable, ranged from 0.004 to 2.5 but mean (0.9) and median values (0.8) were similar]. In contrast inclusion of a case with zero medication increased R^2 tenfold.

Male Subjects

There were no significant differences between groups for age, bone-age, Tanner-rating, and weight, except that the OCD group was lighter than the CON-M group ($t = -3.1$, $p < .01$). There were no significant differences between hormone measures taken in the first and second samples.

Covariance analysis. Analysis of E2, PROG, TE, and DHEAS measures in SCH-M, OCD, and CON-M subjects showed higher DHEAS levels in the SCH-M than in the OCD or CON-M group (Table IV). Other hormone measures did not differ. CON-M and OCD levels were similar throughout.

TABLE IV. HORMONE LEVELS IN MALE SUBJECT GROUPS

	Age	Bone age	Tanner level	Weight (kg)	E2 (pg/ml)	PROG (ng/ml)	TE (ng/ml)	DHEAS (μg/ml)
SCH-M $n = 11$	18.4 (3.5)	18.6 (3.4)	4.73 (0.56)	69 (13)	16.10 (3.57)	1.05 (0.53)	4.70 (1.20)	3.94*† (1.92)
Range	15.1–24.3	14.0–24.0	4.0–5.5	53–101				
CON-M $n = 13$	17.6 (2.9)	17.2 (3.2)	4.69 (.52)	74 (12)	20.30 (6.58)	1.41 (1.10)	5.45 (1.34)	1.94 (1.21)
Range	15.2–23.2	13.5–23.0	4.0–6.0	55–101				
OCD $n = 7$	16.9 (1.9)	16.8 (2.1)	4.00 (1.04)	57 (13)	18.49 (3.20)	1.35 (0.61)	5.84 (2.79)	1.76 (0.88)
Range	14.0–19.2	13.5–19.0	3.0–5.5	45–83				

SDs are in parentheses.

* MANOVA $F(8,50) = 3.27$, $p < .005$; MANCOVA $F(8,42) = 2.34$, $p < .04$; E2: $F(2,24) = 0.84$, $p = .45$; PROG: $F(2,24) = 0.49$, $p = .62$; TE: $F(2,24) = 2.22$, $p = .13$; DHEAS: $F(2,24) = 6.55$, $p < .006$,

† Scheffe SCH > OCD, SCH > CON $p < .01$)1:

(DHEAS for five paranoid vs. six nonparanoid diagnoses 3.8 vs. 4.2 μg/ml).

Correlational analysis. Across groups chronological age correlated with bone age, Tanner-ratings and weight ($r = +0.96, 0.51, 0.46$; $p < .01$, respectively; Table III). In CON-M DHEAS levels correlated with Tanner-ratings and E2 levels ($r = +0.58$, $p < .04$); further, E2 levels were related to PROG levels and age ($r = +0.57$, $p < .05$; $r = +0.81$, $p < .001$, respectively), but not other developmental measures. No such relations were evident in the SCH-M group. Here only the levels of E2 and TE correlated ($r = +0.62$, $p < .04$). Within the SCH-M group developmental measures did not correlate with any hormone measure, which suggests a slight disruption in steroid metabolism and the control of development. There were no correlations between DHEAS levels and illness severity or medication. E2 levels were weakly related to severity ($r = +0.54$, $p < .09$) but not to medication ($r = +0.04$).

Regression analysis. Analysis with DHEAS as dependent variable showed developmental measures contributed similarly to the variance across groups (33%), within SCH-M alone (35%) and within CON-M alone (39%). Bone-age made the major contribution across groups (21%, $p < .01$) but not within SCH-M (21%, $p = .16$). The Tanner-rating was important across groups (6%, $p < .05$) and in CON-M (34%, $p = .03$). BPRS and medication in the SCH-M group contributed only 2% and 5%, respectively ($p > .5$).

DISCUSSION

Female Hormone Changes

Confirming the first part of our hypothesis, young female psychotic patients (SCH-F), with onset as teenagers, showed lower E2 levels than a developmentally matched healthy group compared in an analysis of variance with and without covariates for developmental age, illness severity and medication. Unexpectedly the SCH-F group showed higher levels of TE. Regression analysis showed that neuroleptic medication was more related to TE than E2 levels.

We have found three standardised E2 samples (14%) from SCH-F patients which overlapped with those from the CON-F group; one came from a neuroleptic-free subject and two from subjects aged >24 years. At the lower end of the scale four SCH measures overlapped with the highest from the women taking contraceptives. However, low E2 levels in the SCH-F group were not restricted to teenagers: we found values of 0.20 and 0.48 in subjects aged 29 and 30 years, respectively.

We also found normal standardized values of 0.87 and 1.26 (26–40 pg/ml) in two healthy premenarchical subjects aged 12 and 14 years. Absolute hormone levels from only 2 CON-F subjects, but from 15 of 22 SCH-F samples were in this range. We conclude that the drop in E2 levels in the SCH-F group is not as severe as that achieved by contraceptives and that low E2 levels in SCH-F patients are not adequately explained as an effect of neuroleptic medication.

Male Hormone Changes

With regard to the second part of our hypothesis, young male psychotic patients showed similar E2 and TE levels to developmentally matched OCD patients and healthy controls. The first result (E2) was expected but the second (TE) was not. But the SCH-M group showed distinctly higher levels of DHEAS.

Our negative findings for E2, TE, and PROG in males should not be over-interpreted. A report of increased TE levels specific to male schizophrenics rather than those with

affective disorder (Mason et al., 1988) found the difference was largely due to the paranoid subjects. We found no such subgroup differences (see legend of Table IV).

Methods

Because of the difficulties inherent in this type of study we caution against generalization until the results are replicated. The number of patients was small, although adequate for an exploratory study where both male and female psychotic subjects each had two comparison groups. Difficulties are met with in agreeing on standard values for steroid hormones that are fluctuating across potentially irregular cycles in subjects that may not be sexually mature. (The use of thermometers is not practical in adolescent patients.) Yet we believe that by juxtaposing information from the ward staff, patient and measures of LH and FSH, by using a range of developmental measures and the use of repeated sampling we reduced the sources of error in determining menstrual and developmental stages to a manageable minimum. Evidence for this may be found in the similarity of standardized E2 values between samples and the expected relationships of developmental variables to hormone measures in the healthy subjects.

Progesterone

The lack of differences for PROG in either sex is remarkable, considering that gonadal steroid changes are interdependent and dopaminergic agents affect plasma PROG levels (Goiny et al., 1986). These authors also noted that dopaminergic agents did not alter TE levels in male or female dogs. This is interesting as we found that medication played a significant role in the rise of TE levels in female psychotics, but not in males who received higher doses.

The absence of PROG changes in our patients, who showed high levels of prolactin (particularly those on "typical" neuroleptics, results not shown), does not support the claim that impaired PROG synthesis is associated with hyperprolactinemia (McNatty et al., 1974) and contributes to menstrual dysfunction in psychiatric patients (Beumont & Bergen, 1982). This supports our contention that the differences in hormone levels cannot entirely be explained by treatment-related effects.

DHEAS (Adrenal Androgen)

As DHEAS levels peak in late puberty (Hopper & Yen, 1975; Orentreich et al., 1984), it is not surprising that our measures were higher than in older populations (Schneider et al., 1992), but like this report, levels tended to be higher in males than females. While neuroleptic treatment can increase DHEAS levels in postmenopausal women (David et al., 1988) and high levels of prolactin can increase the levels of adrenal androgen precursors (Giusti et al., 1978), we found increased DHEAS levels in the SCH-M but not the medicated SCH-F group, despite prolactin increases in both sexes.

Increased DHEAS levels may interfere with steroid metabolism and increase E2 levels (James et al., 1983). But we found markedly lower E2 levels in the SCH-F and no E2 increase in the SCH-M group. Several factors can influence steroid metabolism, but we note that weight (reflecting adipose tissue) did not differ between groups and did not correlate with hormone measures. Regression analysis implicated bone-age as the most important developmental factor while illness severity and medication played lesser roles.

Our DHEAS measures were similar to those reported by Tourney and Erb (1979), but where they saw a morning decrease in males we saw an increase. Their patients, however, differed in being unresponsive to neuroleptics and having been in hospital for

over 4 years. Further, it is curious that their control DHEAS levels were so high in a group clearly older than our own. Considering that treatment of healthy subjects with DHEAS may increase outgoing and aggressive aspects of behavior (Sands, 1954) and that DHEAS levels peak in adolescence, it is likely that high levels in adolescent male psychotics reflect an exaggeration of responses typical for this age to the conflict that may have contributed to their initial decompensation.

E2 and Medication

We had expected that the neuroleptic dose would exert a larger effect than was the case. There was a minor influence on E2 levels in the SCH-F and on DHEAS levels in the SCH-M groups and a larger effect on TE levels in SCH-F patients.

In support of our contention that we are seeing illness-related changes superimposed on medication effects is the following: 1) There are gender-specific effects; 2) the effects are similar for unmedicated patients in their first episode and older ones after several episodes and a variable medication history (Table I); 3) the presence of a medication effect on TE levels in SCH-F renders a general procedural error as unlikely; further our results confirm the absence of an effect of dose on TE levels in male schizophrenics (Rinieris et al., 1989; Siris et al., 1980); and 4) high levels of prolactin, impaired PROG synthesis and menstrual dysfunction do not seem necessarily linked (see above).

Hypotheses: E2, Development, Dopamine, and Perinatal Edema

What then characterizes these hormonal differences? In healthy women weight (presumably reflecting adipose tissue) was related to E2 and TE levels. In the SCH-F group weight was less important for E2 measures: sexual maturity was more important for TE measures. An explanation of the variance in E2 measures is not among these factors. In contrast a significant proportion of the TE variance lay with measures of illness severity which is consistent with the TE increase being a consequence of the illness.

What mechanism could explain an effect of E2 on vulnerability to psychosis? Studies of psychosis associated with menses, child birth, or menopause imply that a change, rather than low levels of gonadal steroids per se, constitutes a risk factor. Taking the contraceptive pill is associated with inappropriate mood but not psychosis. An increased incidence of psychosis in women when E2 levels fall could reflect the unmasking dopamine receptors established under higher levels of the neuroleptic-like steroid (Häfner et al., 1989). But in view of the potential contribution of prenatal subclinical brain insult to the risk of developing psychosis (e.g. Bracha et al., 1992), we suggest another possibility.

Gonadal steroids can influence cerebral blood flow by interaction with angiotensinogen and vasopressin. Attella and colleagues (1987) found that high levels of gonadal steroids in pseudopregnant rats protected against cognitive impairment following prefrontal brain-lesion and that these animals showed less edema. The report also discussed a more rapid recovery of female animals after limbic and striatal damage. Also relevant to our proposal is the increased risk of hypertonia, thromboemboly, and cerebrovascular insult for women taking contraceptive preparations over a prolonged period (Carr & Wilson, 1987). It is conceivable that drops in steroid levels may not only unmask dopamine receptors but also the results of small but less specific insults to central nervous tissue.

We conclude with two recommendations for further study. First, we note that serum TE or TE/E2 ratios are related to the tendency for left-handedness (Hassler et al., 1992; Tan, 1991). While the claim for increased left handedness in psychotic populations remains controversial (Taylor, 1987), both features could point towards an unusual later-

alization of brain function (e.g., some types of affective disorder, Wexler et al., 1989). It would be valuable to link hormonal measures in psychotic patients with performance on tasks demonstrated to rely heavily on left or right hemisphere function. Our second proposal is that in view of widespread reporting of menstrual dysfunction, vulnerability to dyskinesia and low E2 levels, that the possibility of high-dose E2 replacement be explored for its potential remedial effect on these features and on the psychotic symptoms of female patients (cf. Campbell & Whitehead, 1977; Fillit et al., 1986; Glazer et al., 1985; Hamilton, 1982; Riecher-Rössler & Häfner, 1993).

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