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Prolactin and estradiol serum levels in unmedicated male paranoid schizophrenia patients

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Abstract

There is evidence for the involvement of the endocrine system in schizophrenia. This involment was widely investigated in female patients.

In the current study, we examined prolactin and estradiol serum levels in hospitalized unmedicated men with first-episode and recurrent schizophrenia and then tested possible correlation with various subtypes of the disease. In addition, the estradiol and prolactin levels were compared with a healthy control group.

The serum samples were assessed the morning following admission in fifty-seven schizophrenia male patients.

There was a significant difference in prolactin serum levels between the paranoid and "nonparanoid" schizophrenia subgroups. However, no significant differences were found in estradiol serum levels between schizophrenia subtypes or between the patients and their healthy counterparts. Finally, a significant and positive correlation was found between the prolactin and estradiol levels in the paranoid subgroup alone. Thus, it appears that low estradiol levels are associated with low prolactin levels, alleged hyperdopaminergic tone and psychotic breakdown in paranoid schizophrenia. The results of the present study further support our previous report of the association between prolactin serum levels and the schizophrenia cluster subtypes, indicating a different dopaminergic activity for the various forms of the disease.

Keywords: Estradiol; Nonparanoid; Paranoid; Prolactin; Schizophrenia subtypes

1. Introduction

The nuclear process of schizophrenia shows considerable differences between men and women in age and symptoms at onset of the illness. Moreover, these differences are apparent during the early course of the disease, in the first psychotic breakdown and in the medium-term evolution (Aleman et al., 2003; Spauwen et al., 2003; Hochman and Lewine, 2004). Onset of schizophrenia occurs during the reproductive period in more than 80% of those affected. There are increased levels of estrogen and testosterone in the brain and periphery during puberty and throughout the reproductive period. Women become ill with schizophrenia 3 to 4 years later than men (Konnecke et al., 2000; Riecher-Rossler et al., 1994). Estrogens are thought to delay the onset of schizophrenia in females by raising the vulnerability threshold for this disease (Riecher-Rossler et al., 1994). Specifically, lower estrogen levels in psychotic women may increase their vulnerability to psychosis (Oades and Schepker, 1994). For schizophrenic women of reproductive age, lower levels of estrogen were found to be associated with more severe negative symptomatology. Recently, these levels were associated with reduced performance in cognitive function, especially verbal performance and executive functioning (Ko et al., 2006).

Men with schizophrenia have a somewhat inferior response to treatment and a generally poorer prognosis than women. One of the

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Table 1
Demographic data of the participants

		Male	Admission status		Age (years)	
		N	1st episode	Recurrent	Mean	SD
Schizophrenia subtypes	Paranoid	31	17	14	36.03	11.02
	Schizoaffective	12	7	5	36.5	8.21
	Disorganized	14	7	7	30.07	8.7
	Control	32	–	–	35.59	10.74
	Total:	89	31	26		

mechanisms of enhanced susceptibility in men is thought to be the weakness of protective dopaminergic estrogen inhibition (Seeman, 1982). Evidence suggests the estrogens may play a role in various mental and neurodegenerative diseases (Bergemann et al., 2005; Cyr et al., 2002). They exert profound effects on mood, mental state and memory by acting on both "classical" monoamine and neuropeptide transmitter mechanisms in the brain (Fink et al., 1996).

17-β Estradiol possesses neuroprotective properties (Green and Simpkins, 2000; Sawada et al., 2000). These may be relevant for the course of schizophrenia and confer an explanation for the pronounced gender differences, with respect to progression and therapeutic response of the disease (Rao and Kolsch, 2003). Chronic estradiol treatment was found to reduce the sensitivity of D2-dopamine receptors in the mesolimbic dopamine system (Di Paolo et al., 1981; Gordon et al., 1980) and to induce down-regulation of dopamine neurotransmission (Hafner et al., 1991b), as was shown both in animals and in a clinical study (Riecher-Rossler et al., 1994). However, there is some evidence of the modulatory effect of estrogen on the dopamine system in a manner similar to neuroleptics, though some inconsistencies exist in the literature (Lindamer et al., 1997).

In our previous study (Segal et al., 2004) we found a significant association between prolactin serum levels and schizophrenia subtypes in unmedicated patients with "low-normal" rates for the paranoid subtype, intermediate for the schizoaffective subtype and "high-normal" for the disorganized ones. These findings suggest differences in dopaminergic tone between the schizophrenia subtypes, and support the clinical and the neuropsychological individuality of disease subtypes.

The present study attempts to assess the 17-β estradiol and prolactin serum levels in a new group of different diagnosis subtype of unmedicated schizophrenia male patients. We will investigate eventual differences in estradiol serum levels in schizophrenia subtypes and try to correlate between prolactin and estradiol levels within each form of the disease.

2. Materials and methods

The subjects were 57 admitted unmedicated 1st episode and recurrent male schizophrenia patients, and 32 control subjects (compared with experimental groups) composed of the hospital staff (Table 1). The recurrent admitted patients had received no oral antipsychotic treatment for at least three months and no depot antipsychotics for at least 6 months. Exclusion criteria were physical illness, including any neurological or endocrine pathology and alcohol or drug abuse.

Table 2
PANSS subscales description of mean±SD scores of positive, negative symptoms, and general psychopathology of the schizophrenia patients

	N	Positive symptoms	Negative symptoms	General psychopathology
Paranoid	31	22.70±5.38	17.42±7.3	46.45±9.94
Schizoaffective	12	24.83±5.67	17.25±9.33	48.58±13.98
Disorganized	14	20.5±8.76	24.5±7.15	47.21±12.92

After a complete description of the study to the subjects, written informed consent was obtained from all the participants.

The diagnosis of schizophrenia and of its subtypes was made according to DSM-IV criteria (APA, 1994) using The Structured Clinical Interview for DSM-III-R-SCID (Spitzer et al., 1992) by at least two senior psychiatrists blind to prolactin and estradiol serum levels. Half of the schizoaffective patients were "schizomanic", whereas the second half composed of "schizodepressed".

The severity of paranoid symptoms was evaluated by "The Maine paranoid and nonparanoid scale" (Magaro et al., 1981). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was also used to assess the severity of various schizophrenia symptoms (Table 2).

Blood samples for the determination of serum prolactin and estradiol levels were collected between 8 and 9 A.M., prior to any medication in the first morning following admission. Estradiol serum levels were evaluated by the IMx Estradiol assay — a Microparticle Enzyme Immunoassay (MEIA) for the quantitative measurement of estradiol in human serum and

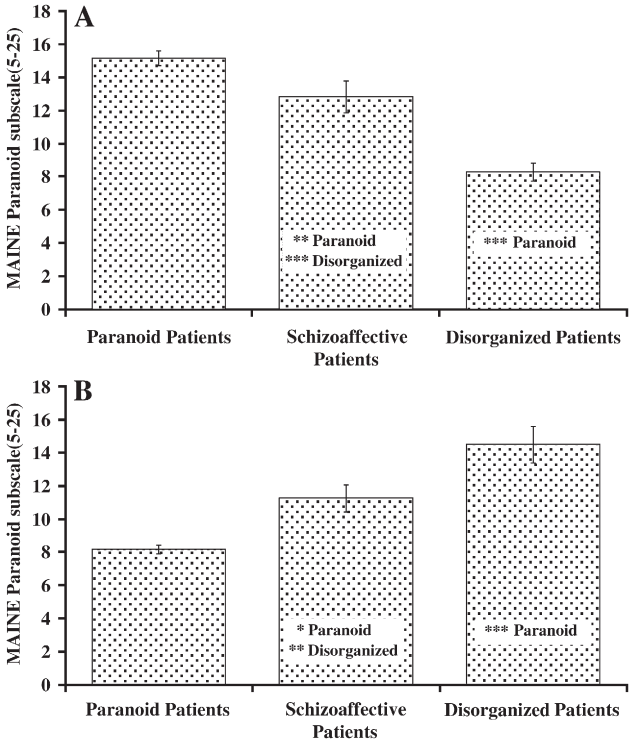

Fig. 1. (A) MAINE paranoid subscale scores were in accordance with the diagnosis of schizophrenia subtypes, with the highest score for the paranoid patients followed by the schizoaffective, and the disorganized patients (***$P<0.0001$; **$P<0.031$). (B) A reversed order was found in the MAINE nonparanoid subscale score (***$P<0.0001$; **$P<0.008$; *$P<0.003$).

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plasma (AxSYM Estradiol assay, 2001). The sensitivity of the IMx Estradiol assay was calculated to be 25 pg/ml and was determined through statistical evaluation of 28 individual assay runs. Of the assay run, 96.4% had calculated sensitivities less than or equal to 25 pg/ml.

For each of the 28 individual assay runs, sensitivity was determined by assaying the IMx Estradiol Calibrator A (0 pg/ml) in replicates of ten. The concentration for each run was determined by calculating the mean rate, and using that calculated rate to determine the concentration of the 10 IMx Estradiol from the calibration curve.

The specificity of the IMx Estradiol assay was determined by studying the interference of triglycerides (up to 1981 mg/dl), hemoglobin (up to 1000 mg/dl) and bilirubin (up to 20 mg/dl). Bilirubin, hemoglobin and triglycerides, at the stated concentrations, had no effect on the determinations of IMx Estradiol values.

Prolactin serum levels were assessed by the Abbott AxSYM system prolactin assay — a Microparticle Enzyme Immunoassay (MEIA) for the quantitative measurement of prolactin in human serum and plasma (AxSYM Prolactin assay-a, 1997).

The sensitivity of the IMx Prolactin assay was calculated to be better or equal to 0.6 ng prolactin/mL. This sensitivity is defined as the concentration at two standard deviations above the Prolactin Calibrator A (0 ng prolactin/mL) and represents the lowest measurable concentration of prolactin that can be distinguished from zero.

For the specificity of the assay serum specimens containing 47–73 ng/mL prolactin were supplemented with growth hormone (1000 ng/mL and were shown to have 0.215% cross-reactivity.

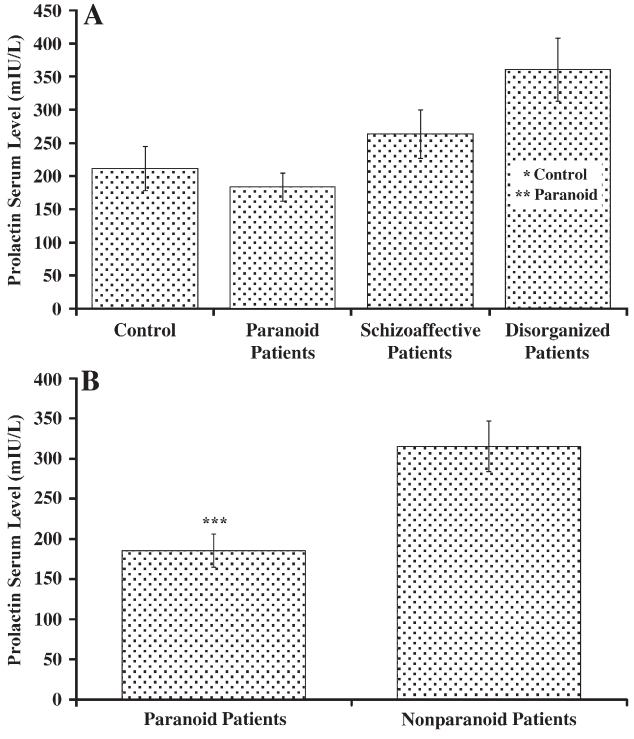

Fig. 2. (A) Higher prolactin levels were found in the disorganized group compared with the control (*$P<0.03$) and the paranoid groups (**$P<0.007$). (B) Likewise, lower prolactin level was found in paranoid versus nonparanoid patients (***$P<0.001$).

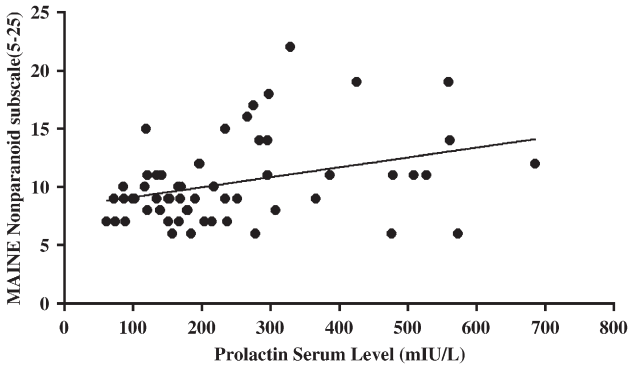

Fig. 3. Prolactin serum levels were positively and significantly correlated with the MAINE nonparanoid subscale score ($r_p=0.345$, $P<0.009$).

No detectable cross-reactivity with luteinizing hormone (5000 mIU/L), follicle stimulating hormone (20,000 μIU/mL), human chorionic gonadotropin (100,000 mIU/L) or human placental lactogen (100,000 ng/mL) was observed.

Blood was centrifuged in glass tubes and plasma was stored in plastic tubes at −80 °C until both prolactin and estradiol assays were completed.

The study was approved by the Mazra Ethical Board.

2.1. Statistical analysis

One-way analysis of variance (ANOVA) followed by Scheffe' post-hoc multiple comparison test, as well as student's *t*-test were used as indicated.

In order to assess the relations between different measures, Pearson's correlation was performed. All tests were two-tailed. The results are presented as mean±S.E.M. or SD.

3. Results

The demographic data of the participants is presented in Table 1.

There was a significant difference in MAINE paranoid subscale score between three-schizophrenia subgroups [$F(2,54)=35.94$, $P<0.0001$), with the highest score for the paranoid group (15.16±2.46) followed by the schizoaffective (12.83±3.18) and the lowest for the disorganized group (8.28±1.93), (Fig. 1A).

In addition, there was a significant difference in MAINE nonparanoid subscale score between the three schizophrenia subgroups [$F(2,54)=30.81$, $P<0.0001$), with the highest score for the disorganized group (14.5±3.95) followed by the schizoaffective (11.25±2.7) and the lowest for the paranoid group (8.16±1.48), (Fig. 1B).

Table 3
Estradiol serum levels of the schizophrenia patients and the control groups showed no significant differences

		Estradiol serum level (mIU/L)	
	N	Mean	SD
Paranoid	31	28.61	9.75
Schizoaffective	12	28.00	9.32
Disorganized	14	25.29	7.29
Control	32	28.25	10.14

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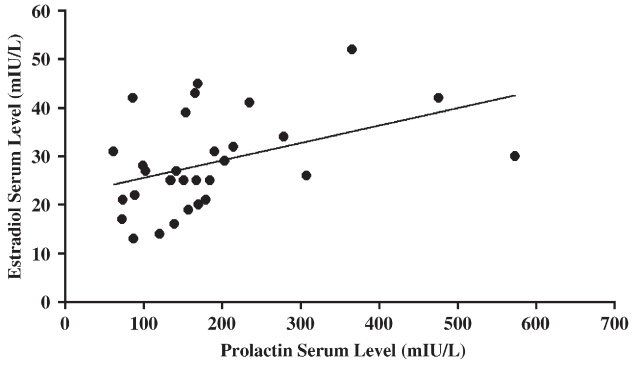

Fig. 4. Prolactin serum levels were positively and significantly correlated with the estradiol serum levels only in the paranoid patients group (r_p=0.422, P<0.018).

A significant difference in prolactin serum levels was found between the schizophrenia subtypes and the control groups [F(3,85)=4.74, P<0.004]. Post-hoc Scheffe' test revealed significant higher prolactin levels in the disorganized group (360.43±171.11) compared with the control (211.51±181.68; P<0.03) and the paranoid (183.51±114.93) groups (P<0.003; Fig. 2A). Likewise, a significant difference in prolactin level was found between the paranoid and the "nonparanoid" (schizoaffective plus disorganized) patients [t(45)=3.58, P<0.001; Fig. 2B].

A correlation was calculated in order to examine the possible difference in prolactin serum level of the paranoid, schizoaffective and disorganized patients and their scores in MAINE subscale. A significant positive correlation was found between the prolactin serum level and MAINE nonparanoid subscale score [r=0.345, P<0.009] (Fig. 3).

No significant differences in estradiol serum levels were found between all groups (Table 3). However, when examining the correlation between prolactin and estradiol serum levels within each schizophrenia subtype, we found a significant correlation only in the paranoid subtype [r=0.422, P<0.018; Fig. 4].

There were no significant differences between the first episode and the recurrent patients in prolactin and estradiol serum levels, as well as in MAINE paranoid and nonparanoid subscales. However there was a significant difference in the age (first episode: 31±8.97, recurrent: 39.03±9.87; P<0.002). The relatively older age of first episode schizophrenia patients could be explained by the predominance of paranoid and schizoaffective cases, characterized by later onset compared with the disorganized ones (Kendler et al., 1994; Schurhoff et al., 2004).

4. Discussion

There has been considerable interest in the possibility that stimulated or basal prolactin concentrations might differentiate schizophrenics, or at least a meaningful subgroup of schizophrenics from normal subjects (Davis et al., 1985). Dopamine tonically inhibits prolactin release (Warner et al., 2001). Despite this, there has been no clear evidence that baseline prolactin levels are abnormal in unmedicated schizophrenia patients (Rubin, 1987) or after withdrawal from neuroleptics (Green et al., 1990). A study that examined unmedicated schizophrenia patients and normal counterparts (Kuruvilla et al., 1992) found no significant differences between the serum prolactin levels of males and females, either among the patients or the control subjects. In medicated patients, Faraone et al. (1987) showed that neuroleptic and prolactin levels did not discriminate schizophrenia patients who relapsed from those who did not relapse. In the remitted patients who relapsed at least once during the study period, neuroleptic and prolactin serum levels were lower before the relapse episodes than before the stable periods.

Previous investigations suggested changes in prolactin activity pattern during exacerbation of chronic illness, with no special emphasis for the schizophrenia subtypes (Davis et al., 1985; Thaker et al., 1989; Kirkpatrick et al., 1992). Hietala et al. (1999) postulated the possible presence of subcortical dopaminergic hyperactivity in paranoid schizophrenia.

The results of the present study confirm our previous reports on the alleged different dopaminergic turnover in paranoid versus "nonparanoid" schizophrenia, as reflected by the significant differences in prolactin serum levels between the two groups (Segal et al., 2004). Specifically, the prolactin levels of the disorganized patients were apparently higher than that of the paranoid ones and of the control group. A possible relative dopaminergic hypoactivity in disorganized schizophrenia could explain this finding.

Previous studies provide only limited data regarding gonadal function in psychotic men. Taherianfard and Shariaty (2004) found that serum concentrations of estradiol, progesterone and cortisol were significantly lower in male schizophrenic patients before treatment, during treatment and after recovery, in comparison with healthy subjects. Huber et al. (2005) reported low estradiol serum level in schizophrenia male patients compared to controls. However, we could not demonstrate significant differences in estradiol serum level between the three investigated subtypes (nor in the dichotomy of paranoid versus "nonparanoid" cases) of schizophrenia men and the control group of healthy volunteers. Whilst Huber et al. (2005) examined schizophrenia patients with antipsychotic treatment, our study consisted of unmedicated patients. Thus, the decrease in estradiol serum level reported by Huber et al. (2005) may be attributed to the elevation of prolactin levels due to the antipsychotic treatment.

Estrogen also shows dose-dependent effects (Di Paolo et al., 1981; Hafner et al., 1991a): Higher doses rapidly stimulate the production of prolactin from the anterior pituitary (Di Paolo et al., 1982), whereas lower doses may have the opposite effect (Kulkarni et al., 2001). These findings are in accordance with the correlation between prolactin and estradiol serum levels that we found only within the paranoid subtype.

Estrogen may be impacting on psychotic symptoms via an interaction with prolactin that has been shown to modulate the biphasic effect of estrogen administration on D2 receptors (Di Paolo, 1994). The reduced prolactin levels in the paranoid patients compared to the schizoaffective and disorganized forms of schizophrenia seem to confirm our hypothesis.

To the best of our knowledge, the current study is the first to examine both prolactin and estradiol serum levels in unmedicated

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schizophrenia male patients, and suggest a specific relation between the two hormones particularly in paranoid schizophrenia.

Though our present findings refer to peripheral circulating prolactin and estradiol levels, there appear to illustrate central dopamine activity. Use of brain imaging technologies may indicate this activity more directly, but these procedures are very difficult to conduct in acute psychotic unmedicated patients. The same reasons limited our capacity to recruit a greater number of schizophrenia subtype subjects. Despite these difficulties, the use of a simple prolactin and estradiol measure may subserve as a supportive tool during the diagnosing process of schizophrenia.

Thus, the present findings together with our previous report (Segal et al., 2004) may enhance the diagnostic process of schizophrenia subtypes.

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