Serum prolactin levels in unmedicated first-episode and recurrent schizophrenia patients: a possible marker for the disease’s subtypes

Michael Segal,*, Avi Avital, Marina Rojas, Noemi Hausvater, Sergio Sandbank, David Liba, Leonardo Moguillansky, Ilana Ta, Abraham Weizman

Flugelman’s (Maza) Mental Health Medical Center, Doar Na Ashrat, Acre 25201, Israel
Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel
Research Unit, Gehah Psychiatric Hospital, Petach Tiqva, Israel
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Received 9 May 2003; received in revised form 23 January 2004; accepted 24 January 2004

Abstract

Various studies indicate that we must consider schizophrenia not as a single disease but as several distinct etiological processes that give rise to characteristic symptoms. In the current study, we aimed to examine prolactin serum levels in unmedicated first-episode and recurrent schizophrenic patients. The prolactin levels were compared among the different schizophrenia subtypes, i.e. paranoid, schizoaffective and disorganized. Prolactin serum samples were assessed on the morning after the admission in 48 first-episode and 38 recurrent unmedicated hospitalized schizophrenia patients. Two psychiatrists made the diagnosis without knowledge of laboratory results and completed the rating scales. Despite all prolactin levels being within or close to the normal range, we found significant differences in prolactin serum levels among schizophrenia subtype patients: the lowest values were for the paranoid type, intermediate for the schizoaffective and the highest for the disorganized patients. The results seem to indicate a pronounced hyperdopaminergic activity in paranoid schizophrenia, suggesting differences in dopaminergic tone between the schizophrenia subtypes, and support the clinical and the neuropsychological individuality of disease subtypes. There were no significant differences in prolactin serum levels of the schizophrenia subtypes between the first-episode and the recurrent patients. It appears that there are constant patterns of dopamine bioactivity in acutely psychotic unmedicated schizophrenia patients, whether the patients are first admitted or recurrent.

© 2004 Elsevier Ireland Ltd. All rights reserved.

Keywords: Dopamine; Prolactin; Paranoid; Schizoaffective; Disorganized

1. Introduction

The classical dopamine hypothesis of schizophrenia proposes that the hyperactivity of dopamine transmission is responsible for the positive symptoms of the disorder.
Most of the affected patients develop schizophrenia during the reproductive period of their lives. This suggests that the disorder could be related to a disturbance in the balance between one or more excitatory and inhibitory factors in the response to the flood of reproductive hormones to the brain and consequent compensatory remodeling of synapses in specific brain areas (Stevens, 2002).

Nowadays, it is widely accepted that there is a relationship between the therapeutic effect of neuroleptic drugs and their ability to antagonize the action of the neurotransmitter dopamine by blockade of the central dopamine receptors (Carlsson and Lindquist, 1963; Creese et al., 1976; Carlsson, 1978; Farde et al., 1988). The role of dopamine in the pathophysiology of schizophrenia is also supported by the psychotomimetic effect of dopamine-enhancing drugs (Carlsson and Lindquist, 1963; Angrist and van Kammen, 1984; Lieberman et al., 1987; Laruelle and Abi-Dargham, 1999; Abi-Dargham et al., 2000).

However, affective flattening, avolition, bradykinesia and anhedonia are considered to be shared symptoms of several diseases like some forms of schizophrenia, Parkinson’s disease and major depression. To the extent that they are phenomenologically similar, a deficiency of dopamine neurotransmission may be seen as a common feature of these diseases (Knable et al., 1997).

One reformulation of the dopamine hypothesis postulates a deficit of dopamine in the cortex, and an excess of dopamine subcortically (Abi-Dargham, 2002).

Grace (1991) proposed that schizophrenia patients suffer from a diminished ‘tonic’ striatal dopamine release, consecutive up-regulation of striatal postsynaptic dopamine receptors and hence increased responses to ‘phasic’ striatal dopaminergic activation due to environmental stress.

Kapur (2003) stated that a central role of dopamine is to mediate the ‘salience’ of environmental events and internal representations. The continuously growing body of evidence indicates that we should consider schizophrenia not as a single disease but as several distinct etiological processes that give rise to characteristic symptoms (Crow, 1982; Peralta et al., 1992; Knoll et al., 1998; Finlay, 2001).

It seems interesting to examine if in addition to the various schizophrenia symptoms, one could refer to the disease’s subtype clusters in relation to dopamine activity. Dopamine tonically inhibits prolactin release (Warner et al., 2001) and there has been a longstanding interest in plasma prolactin as an in vivo indicator of dopamine activity (Chou et al., 1998).

Most of the recent prolactin investigations in schizophrenia evaluate its response to neuroleptic stimulation (Kaneda and Fujii, 2000; Kapur et al., 2000; Melkerson et al., 2001). Zhang et al. (2002) described a close relationship between the improvement in positive symptoms and the change of serum prolactin level before and after risperidone treatment. Moreover, serum prolactin levels at baseline could be used to predict the responses of schizophrenic patients to risperidone (Zhang et al., 2002).

The increase in serum prolactin concentration in patients treated with neuroleptic drugs is well documented, but previous attempts to correlate prolactin concentration with clinical response have yielded inconsistent or conflicting results (Meltzer and Fang, 1976; Rubin, 1987; Van Putten et al., 1991; Nordstrom and Farde, 1998).

Various studies assessed the possibility that stimulated or basal prolactin concentration might differentiate schizophrenic or at least clinically meaningful subgroups of schizophrenic patients from normal subjects (Davis et al., 1985).

Until now there has been no clear evidence that baseline prolactin levels are abnormal in unmedicated schizophrenia patients (Rubin, 1987). However, serum prolactin has a broad range of normal values: 52.8–444 mIU/l (2.2–18.5 ng/ml) for males and 45.6–621.6 mIU/l (1.9–25.9 ng/ml) for females (IMx Prolactin assay, 1997).

The aim of the present study was to assess serum prolactin values in unmedicated, newly admitted first-episode and recurrent schizophrenia patients and to evaluate possible differences in prolactin levels among the diagnostic subtypes of schizophrenia.

2. Methods

2.1. Subjects

The subjects were consecutively admitted first-episode (n = 48) and recurrent (n = 38) unmedicated schizophrenia patients. The recurrent admitted patients had received no oral antipsychotic treatment for at
least 3 months and no depot antipsychotics for at least 6 months. Exclusion criteria were physical illness including any cerebral or endocrine pathology, alcohol or drug abuse and pregnancy.

2.2. Assessment of schizophrenia subtype

The diagnosis of schizophrenia and of its subtypes (P—Paranoid; SA—Schizoaffective and D—Disorganized patients) was made on the basis of DSM-IV criteria (American Psychiatric Association, 1994) by at least two senior psychiatrists, without knowledge of prolactin levels. The severity of paranoid symptoms was evaluated by the Maine Scale of Paranoid and Non-paranoid Schizophrenia (Magaro et al., 1981). The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to confirm the severity of symptoms. After complete description of the study to the subjects, written informed consent was obtained from all participants.

2.3. Serum prolactin collection

Serum prolactin was collected between 08:00 and 09:00 h and prior to any medication. Prolactin serum levels were evaluated by the IMx Prolactin assay (1997)—a Microparticle Enzyme Immunoassay (MEIA) for the quantitative measurement of prolactin in human serum and plasma.

The Ethical Local Board Committee of Flügelman (Mazra) Mental Health Center Accre approved the study protocol.

2.4. Statistical analysis

One-way analyses of variance (ANOVA) followed by Tukey post-hoc multiple comparison tests were used as indicated. For comparisons between two groups, an independent t-test was used. Finally, in order to characterize the relations between different measures, a Pearson correlation was calculated. All tests were two-tailed. The results are presented as means ± S.E. of the means (S.E.M).

3. Results

The demographic data are presented in Table 1. The diagnosis of schizophrenia subtype yielded the following: First episode patients (N=48) with paranoid (N=15) schizoaffective (N=18) and disorganized (N=15) subtypes. Recurrent patients (N=38) with: paranoid (N=11) schizoaffective (N=17) and disorganized (N=10) subtypes.

Table 2 summarizes the scores of the three schizophrenia subtypes among the first-episode and recurrent subgroups on the PANSS paranoid item and the Maine paranoid and non-paranoid subscales.

Two-way ANOVA revealed a significant difference for the PANSS paranoid item (P6-suspiciousness/persecution) score between the three schizophrenia subgroups \([F(2,86) = 37.22, \ P<0.0001]\). A post hoc Tukey test revealed a significant difference between the paranoid, schizoaffective (P<0.0001) and disor-
ganized ($P<0.0001$) groups. There was also a significant difference between the schizoaffective and the disorganized ($P<0.006$) groups.

There was no significant difference between first episode and recurrent patients [$F(1,86)<1$] or the interaction between schizophrenia subtypes and first-episode versus recurrent status [$F(1,86)=1.97$, $P>0.145$].

There was a significant difference in Maine paranoid subscale score among the three schizophrenia subgroups [$F(2,86)=377.83$, $P<0.0001$]. A post hoc Tukey test revealed a significant difference between the paranoid, the schizoaffective ($P<0.0001$) and the disorganized ($P<0.0001$) groups. There was also a significant difference between the schizoaffective and the disorganized ($P<0.0001$) groups.

There was no significant difference between first-episode and recurrent patients [$F(1,86)<1$] or in the interaction between schizophrenia subtypes and admission status [$F(1,86)<1$].

There was a significant difference on the Maine non-paranoid subscale score between the three schizophrenia subgroups [$F(2,86)=33.99$, $P<0.0001$]. A post hoc Tukey test revealed a significant difference between the paranoid, the schizoaffective ($P<0.001$) and the disorganized ($P<0.0001$) groups. There was also a significant difference between the schizoaffective and the disorganized ($P<0.0001$) groups.

Again, there was no significant difference between first-episode and recurrent patients [$F(1,86)<1$] or in the interaction between schizophrenia subtypes and the admission status [$F(1,86)<1$].

We found a significant difference in prolactin serum level between the three schizophrenia subgroups [$F(2,86)=113.61$, $P<0.0001$] with the highest level for the disorganized schizophrenia (439.58 ± 110.54 mIU/l), intermediate level for the schizoaffective (296.01 ± 65.07 mIU/l) and lowest serum prolactin level for the paranoid patients (118.22 ± 33.95 mIU/l). There was no significant difference between first-episode and recurrent patients [$F(1,86)<1$] or in the interaction between schizophrenia subtypes and the admission status [$F(1,86)<1$] (Fig. 1).

In order to define the patients as ‘paranoid’ or ‘nonparanoid,’ we combined the patients from the disorganized and the schizoaffective groups into a ‘nonparanoid’ group within each admission status group.

The non-paranoid group’s score on the Maine non-paranoid subscale was significantly [$t(84)=8.44$, $P<0.0001$] higher than the paranoid group’s score (16.15 ± 2.43, 10.4 ± 3.08, respectively). There was no significant difference between first episode and recurrent patients [$t(84)<1$; 12.35 ± 4.04, 11.87 ±

**Table 2**

Scores on the PANSS paranoid item P6-suspiciousness/persecution and the Maine paranoid and non-paranoid subscales

<table>
<thead>
<tr>
<th>Schizophrenia subtypes</th>
<th>PANSS P6</th>
<th>‘Maine paranoid’</th>
<th>‘Maine non-paranoid’</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
</tr>
<tr>
<td>Admission status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>5.80</td>
<td>0.77</td>
<td>16.27</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>4.78</td>
<td>1.31</td>
<td>12.33</td>
</tr>
<tr>
<td>Disorganized</td>
<td>3.27</td>
<td>1.39</td>
<td>8.47</td>
</tr>
<tr>
<td>Recurrent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>5.82</td>
<td>0.75</td>
<td>16.00</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>3.88</td>
<td>1.50</td>
<td>11.35</td>
</tr>
<tr>
<td>Disorganized</td>
<td>3.50</td>
<td>0.71</td>
<td>8.20</td>
</tr>
</tbody>
</table>

Fig. 1. Prolactin serum levels of three schizophrenia subtypes, across the admission status (***P<0.0001**).
3.8, respectively) or in the interaction between schizophrenia dichotomy subtypes and the admission status \( t(24) < 1; 16.27 \pm 2.76, 16 \pm 2, \text{ respectively} \) (Fig. 2).

Finally, the prolactin level of the non-paranoid group was significantly \( t(78) = 14.94, P < 0.0001 \) higher than that of the paranoid group (355.83 \( \pm \) 111.83 mIU/l, 118.22 \( \pm \) 33.95 mIU/l, respectively). There was no significant difference between first-episode and recurrent patients \( t(84) < 1; 283.73 \pm 145.57, 284.33 \pm 146.554, \text{ respectively} \) or in the interaction between schizophrenia dichotomy subtypes and the admission status \( t(58) < 1; 359.36 \pm 107.69, 351.51 \pm 118.62, \text{ respectively} \) (Fig. 3).

A Pearson correlation was calculated to relate the difference in serum prolactin level of the paranoid, schizoaffective and disorganized patients to their Maine P2 scores. A significant negative correlation was found between the prolactin serum level and the Maine P2 score \( r = -0.507, P < 0.0001 \); Fig. 4).

4. Discussion

The current study shows a significant difference in prolactin levels Maine P2 scores between three schizophrenia subtypes, with the lowest level in the paranoid patients, followed by an intermediate level in the schizoaffective patients, and the highest level in the disorganized patients. Therefore, we can assume that there were no differences in dopaminergic pattern of activity in unmedicated schizophrenia subtypes between the first-episode and the recurrent patients.

![Fig. 2. Maine non-paranoid subscale score of the paranoid and the non-paranoid patients, across the admission status \( t(84) = 7.61, P < 0.0001 \).](image)

These results were correlated with paranoid/non-paranoid diagnoses made on the basis of the Maine scale and the PANSS.

The ‘normal’ range of serum prolactin levels seems to obscure significant differences between specific groups of schizophrenia patients.

As far as we know, there are no previous reports correlating prolactin levels with schizophrenia subtypes. Nevertheless, the possible correlation between serum prolactin levels and various schizophrenia symptoms was previously studied. For example, mean serum prolactin concentration was found to be within the normal range by Meltzer et al. (1974) in 22 unmedicated, acutely disturbed, newly admitted schizophrenic patients. A low plasma prolactin concentration has been reported to be associated with an increased risk of subsequent relapse in patients with schizophrenia (Kirkpatrick et al., 1992). Other authors (e.g. Warner et al., 2001) have reported lower prolactin bioactivity in unmedicated schizophrenic patients compared with normal controls.

Several studies also assessed the correlation between prolactin concentration and various schizophrenia symptoms or outcomes. A clear-cut negative correlation was found between the Comprehensive Psychiatric Rating Scale (CPRS) items assessing hallucinations and serum prolactin levels (Appelberg et al., 2000). However, Otani et al. (1996) did not find any correlation between prolactin levels and psychopathology in schizophrenia as was examined in 56 unmedicated schizophrenic patients. Csernansky et al. (1986) have found that a prolactin index, calculated as the ratio of prolactin levels to noradrenaline, was inversely correlated with paranoid symptoms and
tardive dyskinesia in young treated schizophrenic patients. Keks et al. (1995) evaluated the relationships between basal and hypothalamic-stimulated prolactin concentrations and a number of potentially relevant symptom measures. Basal prolactin was found to be lower in patients without a depressive syndrome and suicidal ideation. The authors interpreted the findings as a link between endocrine measures of dopaminergic function and a subtype of schizophrenic psychosis characterized by the presence of thinking disturbance in the absence of depression.

Many schizophrenic patients are resistant to typical neuroleptics, signifying that neurochemical systems other than dopamine are implicated, especially for those with prominent negative symptoms (Andreasen and Olsen, 1982), and generally the ‘deficit state’ syndromes may not be related to excessive dopamine activity (Davis et al., 1991).

Prolactin responses to the administration of clomipramine (i.v.) and haloperidol (i.m.) were measured in healthy control subjects and in 16 never-treated male patients with DSM-IV diagnoses of schizophreniform or schizophrenic disorders of the paranoid subtype, both before and after 5 weeks of treatment with haloperidol (Angelopoulos et al., 2002). Prolactin responses to haloperidol challenge in the drug-free state were lower in the schizophreniform group than in the control and the schizophrenic groups, but the differences did not reach statistical significance.

Drugs that act as dopamine agonists generally worsen symptoms of schizophrenia (van Kammen et al., 1982; Lieberman et al., 1984; Angrist et al., 1985; Davidson et al., 1987), but the rule is not absolute. There have been reports of schizophrenic patients who developed psychotic symptoms with psychostimulants and others who improved (Wolkin et al., 1996).

All these data support the notion that the effect of dopamine on brain activity depends, in part, on the state of the dopaminergic system.

The significant differences in serum prolactin levels that we found between the unmedicated schizophrenia subtype patients, namely lowest levels in paranoid patients and graded relative increases in the other two subtypes, suggest different hypothalamic-pituitary dopaminergic tone among the various schizophrenia subtypes.

It seems that there could be positive symptoms that are dopamine-dependent and others that are dopamine-independent. Ellinwood et al. (1973) proposed that suspiciousness/paranoia is the most ‘dopamine-dependent’ dimension of psychosis. This hypothesis was supported by the fact that suspiciousness severity was associated at a trend level with intensity of stimulation of D2 receptors by dopamine.

In a recent study, Oades et al. (2002) measured dopamine (DA), noradrenaline (NA), serotonin (5-HT), their three major metabolites and prolactin in the serum of 108 patients with schizophrenia and 63 matched controls. The DA D2-receptor blocking-activity was estimated from a regression of butyrophene displace in striatum in vitro onto positrone emission tomography (PET) reports of receptor binding in vivo. Increased D2-occupancy associated with lower DA metabolism was found in paranoid patients but no relation to relative increases of DA/5-HT and NA metabolism was observed in non-paranoid...
Low DA/5-HT metabolite ratios, high prolactin and low DA metabolism characterized thought-disordered patients.

Abi-Dargham et al. (2000) showed that among positive symptoms, only severity of suspiciousness was associated at a trend level with the effect of alpha-methyl-para-tyrosine on D2 receptor availability after acute dopamine intrasynaptic depletion.

Our study indirectly sustains the symptomatic correlation between suspiciousness and dopamine level in paranoid schizophrenia patients.

Knable et al. (1997) assumed that worsening of negative symptoms may be associated with decreased concentrations of endogenous dopamine. The relatively ‘high-normal’ serum prolactin values that we found in disorganized patients seem to confirm this supposition.

In addition, our results reinforce the argument that schizophrenia represents a heterogeneous syndrome with specific biological markers and could renew interest in the ‘classical’ schizophrenia subtypes. The rapid evaluation of prolactin serum levels could provide supplementary information to the clinical interview on the acutely psychotic new, admitted patient.

Low dopaminergic activity, indirectly assessed by high ‘normal’ prolactin values, might contribute to treatment decisions use low affinity dopamine D2 neuroleptics. In the opposite cases, paranoid patients with putatively high dopaminergic activity could be treated by antipsychotics with high affinity for the dopamine D2 receptors.

Faraone et al. (1987) showed that through the relapse periods, the prolactin levels were lower than the patients were stable and in remission.

Six weeks after discontinuation of medication in 22 subjects with schizophrenia (Kirch et al., 1988), there was a trend towards an increase in the plasma concentration of the dopamine metabolite, homovanillic acid (HVA). The early relapsing patients after neuroleptic discontinuation had lower baseline and the significantly greater plasma HVA levels after discontinuation than non-relapsing ones (Glazer et al., 1989).

When serum prolactin levels were plotted over time (Green et al., 1990), 55% of 22 stable schizophrenia patients who had been withdraw from neuroleptic medication for 3 weeks showed shifting prolactin levels in the shape of a ‘V’ (i.e. a fall in prolactin level preceding an increase) in the early weeks following withdrawal. Subjects with the ‘V’ shape had significantly lower prolactin levels during neuroleptic treatment than those without the ‘V’ shape. The pathophysiological significance of the prolactin ‘V’ pattern was considered uncertain but still was consistent with transient dopaminergic hyperactivity following neuroleptic withdrawal.

According to our present results, a possible explanation of the ‘V’ shape could involve the specific pattern of prolactin secretion for the disorganized subtype, both treated and untreated, with alleged hypodopaminergic activity.

The similarity that we found for prolactin levels between the first-episode and the recurrent sub-types suggests a repetitive secretion pattern of dopamine, specific for the various disease clusters. Dopamine appears to behave in the same parameters for the relapsed cases with no relationship to gender, age of onset of illness, number of psychotic episodes, years spent ill, and prior medication with neuroleptics. The interpretation of the results of the women patients is influenced by the relatively small number of women admitted. Therefore, the results must be confirmed in a greater number of cases.

In summary, the current study seems to provide an approach to the ‘frustrated efforts to find neurobiological abnormalities that are consistently associated with schizophrenia’ (Fenton and McGlashan, 1991).

As a ‘wind of psychotic fire’ (Laruelle and Abi-Dargham, 1999), dopamine seems to be like a storm, like a whirlwind or simply like a vernal breeze.

The present findings, particularly if confirmed by further investigations, strongly suggest different levels of participation of dopamine in the different subtypes of schizophrenia, arguing for distinct neurochemical correlates of clinical subtypes, and raising the possibility of instituting psychopharmacological treatment accordingly.

Acknowledgements

The authors thank Lili Sigal, M.Sc., Eva Belousov, B.A. from the biochemical lab, the nursing staff of the 9th and 10th wards, and the psychiatric residents of Flügelman’s (Mazra) Mental Hospital for their precious help.
References


Abi-Dargham, A., 2002. Recent evidence for dopamine abnormalities in schizophrenia. European Psychiatry 17 (Supplement 4), 341–347.


