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ORIGINAL PAPER

M. Erkan Ozcan · Ramiz Banoglu

Gonadal hormones in schizophrenia and mood disorders

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Abstract There are gender-related differences in the prevalence, course and treatment response characteristics of schizophrenia and mood disorders. Gonadal steroids exert potent effects on mood, cognition and behavior, and there is little doubt that androgens are crucial for differentiating to each gender. Serum level of total testosterone, free testosterone, estradiol and sex hormone binding globulin was measured in 69 medication-free men with either schizophrenia (n = 29) or bipolar I disorder, manic episode (n = 18) or major depressive disorder (n = 22). There was a statistically significant difference in free testosterone level between mania and schizophrenia groups ($p < 0.05$). The higher free testosterone level in the mania group compared to the schizophrenia group found in this study supports further investigation of a potential difference in the hypothalamic-pituitary-gonadal axis between patients with schizophrenia and bipolar I disorder, manic.

Key words testosterone · men · mania · depression · schizophrenia

M. Erkan Ozcan
Mood Disorders Unit
Dept. of Psychiatry
Inonu University Medical School
Malatya, Turkey

R. Banoglu
Dept. of Psychiatry
Ataturk University Medical School
Erzurum, Turkey

Doc. Dr. M. Erkan Ozcan (✉)
Turgut Ozal Tip Merkezi Psikiyatri Bolumu
44069 Malatya, Turkey
Tel.: +90-422/3410-660/5403
Fax: +90-422/3410-728
E-Mail: eozcan@inonu.edu.tr

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Introduction

There is a close relationship between hormones and the central nervous system and also the gender-related differences in the prevalence, course, and treatment response characteristics of several psychiatric disorders including schizophrenia and mood disorders. For this reason, gonadal hormones have attracted the interest of investigators studying the endocrinologic aspects of psychiatric disorders [26]. Several observations such as a greater prevalence of depression [2], and a later onset of schizophrenia [11] among women, and abnormal levels or secretory patterns of androgens in depression [3, 22] and in schizophrenia [7] suggest the potential importance of knowledge of the effects and mechanisms of action of androgens.

Through both non-genomic and receptor-mediated genomic mechanisms, androgens in animals appear to regulate the actions of a wide range of neurotransmitters and neuropeptides [19]. In humans as in animals, there is evidence suggesting the ability of gonadal steroids to influence central nervous system (CNS) structure and function [10, 14, 32]. In men, androgens masculinize brain during early development [33]. They permanently alter the structure or functional potential of the brain when acting on it during brief developmental windows by their organizational effects [23]. Metabolically, dehydroepiandrosterone (DHEA) serves as a precursor for both estradiol (E_2) and testosterone (T) [36]. In target cells, T is converted to two active metabolites: dihydrotestosterone (DHT) and E_2. In many tissues the activity of T appears to depend on reduction to DHT, which binds to cytosol receptor proteins. This steroid-receptor complex is then transported to the nucleus where it initiates transcription events and cellular changes related to androgen action. In brain, T may either itself act at the androgen receptor, or it may be aromatized to produce E_2 which then acts at the estrogen receptor to mediate the effects of androgens [33].

Non-genomic (non-transcriptional) effects of go-

nadal hormones do not depend on gene transcription or protein synthesis and involve steroid-induced modulation of cytoplasmic or cell membrane-bound regulatory proteins, and as in other organs, they modulate protein kinase cascades in the brain [27]. Signal transducing G proteins transduce extracellular signals into various intracellular responses by coupling membrane cell receptors to intracellular second messengers [20]. Modulation of membrane receptors linked to G-proteins by gonadal hormones may explain intracellular Ca^{2+} mobilization and activation of protein kinase C [15]. While T is able to regulate the mitogen-activated protein kinases (MAPK), estrogen treatment of various cell types induces protein tyrosine phosphorylation, which is involved in the recruitment of other non-genomic pathways including MAPK [27].

Limited studies investigating gonadal hormone levels in patients with schizophrenia and mood disorders have yielded inconsistent results. Whalley et al. [35] found significantly increased luteinising hormone (LH) levels in acute mania compared to an acute episode of schizophrenia or controls, and higher prolactin and cortisol levels in mania and schizophrenia compared to control values. Mason et al. [17, 18] compared male inpatients with either schizophrenia or affective disorders, and they found higher level of total T in patients with schizophrenia in both studies. Measuring the levels of free T and sex hormone binding globulin (SHBG) is necessary while studying the profile of gonadal hormones, as it has been demonstrated that high-affinity steroid binding proteins and specifically SHBG modulate the transport of gonadal steroids across the blood-brain barrier [13].

Patients with schizophrenia and mood disorders may display different profiles of gonadal hormones. The goal of this study was to compare serum levels of gonadal hormones in medication-free patients with schizophrenia, mania and depression, and to evaluate potential differences.

Methods and materials

Twenty-nine inpatients with schizophrenia, 22 outpatients with major depressive disorder, and 18 inpatients with bipolar I disorder, acutely manic were investigated in psychiatry clinics of the university hospital located in Erzurum, Eastern Turkey. As the level of gonadal hormones would have been affected by phases of menstrual cycle, pregnancy and childbearing, and menopause, consistent with earlier studies, we did not include women. All patients were men, medication-free for at least a month, and between ages 18–65 years. They met DSM-IV criteria [1] for respective diagnoses. Two psychiatrists (MEO and RB) confirmed diagnoses in consensus. All manic patients were experiencing classic mania, and none of depressives was bipolar. Of patients with schizophrenia, 22 were of the paranoid type, 5 of the undifferentiated type, and 2 of the disorganized type.

After explanation of our purpose and procedures, written informed consent was obtained either from the patient or from a close relative when the patient was deemed unable to provide informed consent. The study was approved by the Committee for Scientific Research at Ataturk University Medical School, and met international standards for patient protection procedures. Patients were started on usual treatment immediately after blood withdrawal. Patients with any co-morbid axis I diagnosis were excluded. Patients with history of substance abuse (including anabolic steroids) or substance dependence in the past year, and patients with past month history of taking any medication that may interfere with hormone levels (including hormones and all psychotropic medications) and also patients with unstable medical condition or brain damage were excluded.

We did not hypothesize that hormone levels differed from healthy control subjects versus patients with schizophrenia or mood disorders. For this reason, we did not include a control group of healthy subjects. To assess the normality of the values obtained in the study, normal ranges in men were taken into consideration. Blood samples (5 ml from each patient) were obtained at the same time (10:00 am) for all patients prior to any treatment including electro-convulsive treatment. Serum total and free T, E_2 and SHBG levels were measured for each patient by the same laboratory. Methods used for the measurement were radioimmunoassay (RIA) for total T, free T and E_2, and immunoradiometric assay (IRMA) for SHBG. For these tests, the following reference ranges were used as normal values in men at our laboratory: total T (270–1070 ng/dl), free T (10–40 pg/ml), E_2 (0–44 pg/ml), SHBG (10–73 nmol/L). The mean age differences between patient groups were compared using a t-test. T-test was performed pairwise. An Analysis of Variance (ANOVA) model was used to compare the hormone levels between the diagnostic groups. The dependent variable in the ANOVA model was the ranked hormone level. The independent variable was the diagnostic group. P-values were obtained comparing the Least Squares Means (LSMEANS) in the ANOVA model.

Results

There was no significant difference in the mean age among the patient groups as shown in Table 1. The mean age ± SD (years) in patient groups was as follows: mania 37.1 ± 11.8, depression 34.8 ± 12.8, schizophrenia 31.8 ± 7.5. Body weight, exercise and smoking habits of the patients in the sample were similar.

The mean level of total T ± SD (ng/dl) in each patient group was as follows: mania 568.2 ± 219.3, depression 579.5 ± 314.4, schizophrenia 520.0 ± 241.6. The mean level of free T ± SD (pg/ml) in each patient group was as follows: mania 26.1 ± 12.9, depression 20.9 ± 7.5, schizophrenia 18.7 ± 7.7. The mean level of E_2±SD (pg/ml) in each patient group was as follows: mania 32.8 ± 19.0, depression 37.1 ± 14.7, schizophrenia 35.7 ± 16.4. The mean level of SHBG ± SD (nmol/L) in each patient group was as follows: mania 53.8 ± 19.9, depression 62.5 ± 24.7, schizophrenia 62.5 ± 26.7. Descriptive statistics for hormones and SHBG levels in groups are presented in Table 2.

The mean hormone and SHBG levels in all groups were within normal ranges. A higher mean free T level in patients currently manic was observed relative to schizophrenia group. This difference was statistically significant ($p < 0.05$). There were no other statistically significant differences among the patient groups.

Table 1 Age distribution (as years) in diagnostic groups

Group	N	Mean	SD
Mania[a]	18	37.1	11.8
Depression[b]	22	34.8	12.8
Schizophrenia[a]	29	31.8	7.5

[a] inpatients; [b] outpatients

Table 2 Descriptive statistics for hormone levels in patient groups

	N	Mean	SD
Total Testosterone (ng/dl)			
Mania	18	568.2	219.3
Depression	22	579.5	314.4
Schizophrenia	29	520.0	241.6
Free Testosterone (pg/ml)			
Mania[c]	18	26.1	12.9
Depression	22	20.9	7.5
Schizophrenia[c]	29	18.7	7.7
Estradiol (pg/ml)			
Mania	18	32.8	19.0
Depression	22	37.1	14.7
Schizophrenia	29	35.7	16.4
SHBG (nmol/L)			
Mania	18	53.8	19.9
Depression	22	62.5	24.7
Schizophrenia	29	62.5	26.7

[c] $p < 0.05$

Discussion

We investigated serum levels of total T, free T, E_2 and SHBG in 69 medication-free men with a diagnosis of schizophrenia, bipolar I disorder, manic episode, or major depressive disorder. While the mean hormone levels were within normal ranges for men in all patients overall, we found higher free T level in the mania group (26.1 ± 12.9 pg/ml) compared to the schizophrenia group (18.7 ± 7.7 pg/ml). This difference between the mania and schizophrenia groups was statistically significant ($p < 0.05$). No other statistically significant difference in levels of total T, E_2, and SHBG were noted between the patient groups. As Mason et al. [18] had done, our approach was reliant upon the criterion of statistical difference in hormone levels between diagnostic subgroups, rather than the supposition that a hormonal measure must show abnormal or pathological value (outside the 'normal range', as used in defining glandular disease), in order to have clinical significance in psychiatric disorders.

Studies investigating gonadal hormone levels in psychiatric patients may have somewhat inconsistent results for several reasons. Measurement of serum T is subject to methodological problems [28]. Rabkin et al. [24] noted the wide range of normal values of total T (270 ng/dl to 1100 ng/dl), and discussed the variability in the range of normal values between laboratories, a problem examined by Boots et al. [5], who reported that the measurement of T by commercially available kits may have limited clinical utility because of the high degree of variability between kits. Another contribution to the inconsistency in the results of gonadal hormone studies may be the differences in the patients' medication status. It has been shown that antipsychotics lead to reduced T levels both in rats [21] and in humans [4, 6]. For this reason, we selected medication-free patients. Sample size is another factor that might affect the results across studies. Testosterone is not equally distributed between the blood stream and CNS [13]. The average cerebrospinal fluid concentration of T was about 1.6% of the concurrent plasma level of T, in a previous animal study [16]. Therefore, free (that is bioavailable) form of T should be considered while assessing its CNS effects. It is likely that including free T measurement in the gonadal hormones we studied, and selecting unmedicated patients contributed to finding different results than earlier studies.

Gonadal hormones have been shown to influence various serotonin functions in humans and animals [12]. A link between testosterone-sensitive receptors and mood disorders is suggested by the finding of Fischette et al. [9] that T, via T receptors, modulates behavioral response to pargyline and the serotonin precursor tryptophan in rats. Studying expression of serotonin receptors in rat brain, Zhang et al. [37] report that their data provide evidence for region-specific sex differences in serotonin receptor subtype 1A [5-HT(1A)R] and 2A [5-HT(2A)R] transcription and concentration in the rat brain, and further suggest a modulatory role of T in particularly 5-HT(1A)R expression. They believe that gender and/or gonadal steroids influence brain serotonergic circuitry, which may underlie sexual dimorphisms in affective state regulation, response to psychopharmacological agents or pituitary-adrenal activation. Sumner and Fink [29] suggest that potent effects of gonadal hormones on mood in the human might be mediated by the action of estrogen on the 5-HT(2A)R and the serotonin transporter (SERT) in brain. Testosterone and estrogen increases significantly the content of 5-HT(2A)R mRNA and SERT mRNA in the dorsal raphe nucleus and the density of 5-HT(2A)R and SERT binding sites in higher centers of the brain [30]. The lack of effect of 5alpha-dihydrotestosterone (5alpha-DHT), a potent androgen which can not be converted to estrogen, suggests that the action of T depends upon its conversion to estrogen by aromatase (CYP19). This may explain why estrogen, but not T or 5alpha-DHT, increases the density of 5-HT(2A)R binding sites in the caudate-putamen, a brain region where CYP19 is scarce [8]. In a recent study, Suzuki et al. [31] demonstrated by using 5-HT-induced platelet intracellular Ca response, that enhanced 5-HT(2A)R function is a specific finding for drug-naive patients with bipolar disorder, but not for schizophrenia or other psychiatric disorders.

The role of estrogens in male physiology has become more evident, as a consequence of the discovery of human models of estrogen deficiency such as estrogen resistance or aromatase deficiency [34]. Inhibition of aromatization in intact male monkeys acutely elevates serum levels of LH [25] which would lead to an increase of T secretion from leydig cells. We suggest further investigation focusing on testosterone level in larger samples of patients with schizophrenia and bipolar disorder.

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