Increased Systemic Cortisol Metabolism in Patients With Schizophrenia and Bipolar Disorder: A Mechanism for Increased Stress Vulnerability?

Nils Eiel Steen, MD; Paal Methlie, MD; Steinar Lorentzen, MD, PhD; Sigrun Hope, MD; Elizabeth A. Barrett, PsyD; Sara Larsson, PsyD; Erlend Mork, PsyD; Bjørg Almås, PhD; Kristian Løvås, MD, PhD; Ingrid Agartz, MD, PhD; Ingrid Melle, MD, PhD; Jens P. Berg, MD, PhD; and Ole A. Andreassen, MD, PhD

ABSTRACT

Objective: The hypothalamic-pituitary-adrenal (HPA) axis seems dysregulated and part of the pathophysiology in bipolar disorder and schizophrenia, but the underlying mechanisms are unknown. Recent evidence indicates that systemic cortisol metabolism influences blood cortisol levels and HPA axis functioning. Our objective was to estimate systemic cortisol metabolism by means of the activity of 5α-reductase, 5β-reductase, and 11β-hydroxysteroid dehydrogenase (11β-HSD) in patients with bipolar disorder and schizophrenia spectrum disorders compared to healthy controls.

Method: Inpatients and outpatients aged 18 to 65 years with *DSM-IV* bipolar disorder (n = 69) or schizophrenia (n = 87) were consecutively recruited to the catchment area–based Thematically Organized Psychosis Research (TOP) study. Healthy controls (n = 169) were randomly selected from statistical records from the same catchment area and were contacted by letter inviting them to participate. Spot urine samples were collected in a cross-sectional manner from November 2006 to November 2008. Urinary free cortisol and cortisone and their metabolites were analyzed with liquid chromatography tandem mass spectrometry and used as indicators of 5α-reductase, 5β-reductase, and 11β-HSD activity.

Results: The combined patient group had increased activity of 5α-reductase, 5β-reductase, and 11β-HSD2 (all $P < .001$) compared to controls. Elevated systemic cortisol metabolism was present in both schizophrenia (5α-reductase, 5β-reductase, and 11β-HSD2; all $P < .001$) and bipolar disorder (5α-reductase [$P = .016$], 5β-reductase [$P = .001$], and 11β-HSD2 [$P = .007$]).

Conclusions: The results indicate increased activity of cortisol metabolism in patients with bipolar disorder and schizophrenia compared to healthy controls and suggest that increased systemic cortisol metabolism is involved in the pathophysiology and stress vulnerability in these severe mental disorders. The findings should be explored further in terms of potential new drug targets, and they add to the physiologic rationale for stress coping strategies in these patient groups.

J Clin Psychiatry 2011;72(11):1515–1521

Submitted: *February 19, 2010; accepted March 29, 2010.*
Online ahead of print: *February 8, 2011 (doi:10.4088/JCP.10m06068yel).*
Corresponding author: *Nils Eiel Steen, MD, Department of Mental Health and Addiction, Oslo University Hospital, 0514 Oslo, Norway (n.e.steen@medisin.uio.no).*

Bipolar disorder and schizophrenia are severe mental disorders, considered to be part of the psychosis spectrum, with overlapping symptomatology and common genetic determinants.[1] The molecular genetic architecture is still mostly unknown, and the pathophysiology remains elusive. Increased hypothalamic-pituitary-adrenal (HPA) axis activation is documented in both disorders.[2–5] This dysregulation is proposed to be part of the pathophysiology in bipolar disorder and schizophrenia,[4,5] is a promising target for pharmacotherapy in bipolar disorder,[6] and seems associated with treatment response in schizophrenia.[7] However, the underlying mechanism of the HPA axis dysregulation is largely unknown. An intriguing possibility is that dysregulation of systemic cortisol metabolism could play a role. This possibility has received little attention, and, to the best of our knowledge, there are no studies on cortisol-metabolizing enzymes in bipolar disorder and schizophrenia.

The HPA axis is an important stress response system and has complex regulatory mechanisms.[8] Both inhibitory and excitatory pathways originating from limbic structures (hippocampus, amygdala, and prefrontal cortex) regulate secretion of corticotropin-releasing hormone and vasopressin from the paraventricular nucleus of the hypothalamus. Corticotropin-releasing hormone and vasopressin stimulate release of adrenocorticotropic hormone from the anterior pituitary, resulting in increased cortisol secretion from the adrenal cortex. Cortisol acts on higher levels of the axis, regulating the activity through feedback inhibition.[8] The HPA axis has a finely balanced equilibrium, and dysregulation could arise from perturbation at any level,[9] including the metabolism of cortisol.

Several enzymes are involved in the metabolism of cortisol. The most important are 5α-reductase, 5β-reductase, and 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 and 2; 5α-reductase and 5β-reductase are rate-limiting enzymes in the liver, catalyzing the irreversible conversion of cortisol to 5α-dihydrocortisol and 5β-dihydrocortisol and of cortisone to dihydrocortisone (5β-reductase). These intermediates are further hydroxylated to form allo-tetrahydrocortisol (aTHF), tetrahydrocortisol (THF), and tetrahydrocortisone (THE), followed by conjugation and excretion in the urine. The enzyme system 11β-HSD interconverts cortisol and cortisone and is a tissue-specific modulator of glucocorticoid receptor exposure to cortisol. The isoenzyme 11β-HSD1 acts mainly as a reductase in vivo, catalyzing the formation of cortisol (active) from cortisone (inactive). It is located in a variety of human tissues and is responsible for hepatic conversion of cortisone to cortisol. The isoenzyme 11β-HSD2 acts as a dehydrogenase, catalyzing the formation of cortisone from cortisol. It is located in mineralocorticoid-responsive tissues, including the kidneys, protecting mineralocorticoid receptors from cortisol binding.[10]

There is recent evidence for systemic 11β-HSD influence on systemic cortisol levels and functioning of the HPA axis. Both isoenzyme type 1 (hepatic) and 2 (renal) show modulatory effects on serum levels of cortisol and cortisone.[11,12] Isoenzyme 11β-HSD1–deficient mice have a relative shift toward inactivating corticosterone (in humans: inactivating cortisol) and demonstrate an abnormal activity of the HPA axis,[13] which is reversed by introducing 11β-HSD1 in hepatic tissue.[14] These interplays make systemic cortisol metabolism an area of interest in disorders with HPA axis dysregulation. There are some studies[15–19] on 5α-reductase, 5β-reductase, and 11β-HSD activity in depression, but these studies show varying results.

Our objective in the present study was to determine the activities of enzymes in systemic cortisol metabolism in bipolar patients, schizophrenia patients, and healthy controls by analyzing urinary free cortisol, cortisone, and cortisol metabolites in order to investigate (1) whether systemic cortisol metabolism is enhanced in bipolar disorder and schizophrenia compared to healthy controls, demonstrated with a shift in 11β-HSD activity toward increased dehydrogenase activity and increased 5α-reductase and 5β-reductase activities, and (2) whether the systemic cortisol metabolism is similar in bipolar disorder and schizophrenia, demonstrated by no differences in enzyme activities.

METHOD

Subjects

Patients were recruited through referrals to the ongoing Thematically Organized Psychosis Research (TOP) study that is carried out by the University Hospitals of Oslo, Norway. Inclusion criteria were as follows: (1) being registered as an inpatient or outpatient in the psychiatric services of any one of the 4 hospitals in Oslo; (2) aged 18 to 65 years; (3) meeting *DSM-IV* criteria for schizophrenia spectrum disorders or bipolar disorders; and (4) being willing and able to give written, informed consent for participation. Exclusion criteria were history of moderate or severe head injury, neurologic disorder, mental retardation, diagnosis of hepatic or renal disorder, thyroid dysfunction, Addison's disease, Cushing's syndrome, or use of corticosteroid medications.

Clinical diagnostic assessments were done by trained clinical research personnel using the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[20] Interrater reliability was good, with an overall κ score of 0.77 (95% CI, 0.60–0.94). The Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C),[21] the Calgary Depression Scale for Schizophrenia (CDSS)[22] (used for 20 subjects with schizophrenia spectrum disorder and 1 with bipolar disorder), the Young Mania Rating Scale (YMRS),[23] and the Positive and Negative Syndrome Scale (PANSS)[24] were used for symptom assessments.

Included in the current analyses were consecutively referred patients with measurements of urinary cortisol metabolites, consisting of a total of 156 patients, of which 87 had a *DSM-IV* schizophrenia spectrum disorder (schizophrenia [n = 67], schizophreniform disorder [n = 9], and schizoaffective disorder [n = 11]), termed here as *schizophrenia*, and 69 had bipolar disorder (bipolar I disorder [n = 37], bipolar II disorder [n = 18], and bipolar disorder not otherwise specified [n = 14]), termed here as *bipolar disorder*. A representative, healthy control group was randomly selected from statistical records from the same catchment area as the patient groups, and the subjects were contacted by letter inviting them to participate. Included in the current analyses were 169 consecutively recruited healthy controls with urinary samples and not using corticosteroid medication. Six urinary samples from the patient group and 1 from the healthy control group were excluded because of technical errors during sampling. Data were collected from November 2006 to November 2008.

Both patient groups showed, on average, only mild depressive and manic symptoms (Table 1). The schizophrenia group had a significantly higher PANSS total score ($U = 742.0$; $Z = -7.6$; $P < .001$), YMRS total score ($U = 2{,}182.0$; $Z = -2.2$; $P = .028$), and IDS-C total score ($U = 1{,}561.0$; $Z = -2.3$, $P = .020$) compared to the bipolar disorder group. The higher score on the YMRS was due to item 8, which measures delusions.

There were between-group differences in distribution of sex ($\chi^2_2 = 9.3$, $P = .009$), with relatively more men in the schizophrenia group compared to the bipolar disorder group. The groups differed in age ($\chi^2_2 = 10.3$, $P = .006$), as the schizophrenia group was significantly younger than the bipolar disorder group ($P = .003$) and the healthy controls ($P = .040$), and the bipolar disorder group was older than the healthy controls ($P = .050$). Time of sampling differed significantly between the groups ($\chi^2_2 = 46.9$, $P < .001$); more controls were screened in the afternoon, with later urinary sampling than the 2 patient groups (both $P < .001$). Time of sampling also differed somewhat between the patient groups ($P = .023$) (median [interquartile range]: bipolar disorder, 10:25 AM [2.00 hours]; schizophrenia, 11:20 AM [2.58 hours]; healthy controls, 1:10 PM [6.08 hours]). There were between-group differences in urinary creatinine ($\chi^2_2 = 18.5$, $P < .001$), with elevated levels in schizophrenia and bipolar disorder compared to healthy controls ($P < .001$ and $P = .040$, respectively). Body mass index, measured in a subset of 125 healthy controls and 146 patients, differed between groups ($\chi^2_2 = 6.8$, $P = .034$), with higher levels in the schizophrenia group compared to healthy controls ($P = .019$). These variables were included in the subsequent analyses of covariance.

In the schizophrenia group, 76 patients (87%) used 1 or more antipsychotics, 25 (29%) used antidepressants, and 8 (9%) used mood stabilizers. In the bipolar disorder group, 34 patients (52%) used 1 or more antipsychotics, 31 (47%) used antidepressants, and 34 (52%) used mood stabilizers (3 had missing data). Forty-one patients (27%) received monotherapy and 93 (61%) used a combination of psychopharmacologic agents, while 19 (12%) used no psychopharmacologic agents.

After the study was completely described to the subjects, written informed consent was obtained from each participants.

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 1. Sample Characteristics According to Study Group

Characteristic	Bipolar Disorder[a] (N = 69), n (%)	Schizophrenia Spectrum Disorders[a] (N = 87), n (%)	Healthy Controls (N = 169), n (%)	*P* Value
Gender, male	30 (43.5)	59 (67.8)[b]	97 (57.4)	.009
	Median (IQR)	Median (IQR)	Median (IQR)	
Age, y	35.0 (19.0)	27.0 (12.0)[b,c]	31.0 (13.0)	.006
Urinary creatinine,[d] mmol/L	9.1 (10.9)[c]	11.1 (8.9)[e]	6.1 (8.0)	< .001
Body mass index,[f] kg/m^2	26.0 (5.3)	26.0 (7.8)[c]	24.2 (4.6)	.034
IDS-C total score	12.0 (17.0)	18.0 (19.0)	NA	.020
YMRS total score	2.0 (6.8)	6.5 (9.9)	NA	.028
PANSS total score	42.0 (10.0)	61.0 (24.0)	NA	< .001

[a]One subject in the bipolar disorder group was assessed with the CDSS, with a score of 3.0. Twenty subjects in the schizophrenia spectrum disorders group were assessed with the CDSS, with a median (IQR) score of 5.5 (6.8).
[b]$P < .05$ vs bipolar disorder.
[c]$P < .05$ vs healthy controls.
[d]Data were missing for 4 subjects in the schizophrenia group and for 2 subjects in each of the bipolar disorder and healthy control groups.
[e]$P < .001$ vs healthy controls.
[f]Data were reported in a subset of 146 patients and 125 healthy controls.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia; IDS-C = Inventory of Depressive Symptomatology, Clinician-Rated; IQR = interquartile range; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale.

The Regional Ethics Committee and The Data Inspectorate approved the study. The biobank was approved by the Norwegian Directorate of Health.

Design and Cortisol Measurements

Within 2 weeks after clinical assessments, patients underwent neuropsychological testing and routine blood withdrawal. On this occasion, urine was sampled and immediately frozen for later analyses of urinary free cortisol (UFF) (reflecting systemic free cortisol), urinary free cortisone (UFE), aTHF, THF, and THE. The healthy controls underwent the same urine sampling, neuropsychological testing, and blood withdrawal procedure.

Allo-THF, THF, THE, cortisol, and cortisone in urine were measured by validated methods developed at the Institute of Internal Medicine, University of Bergen, and the Hormone Laboratory, Haukeland University Hospital, Bergen, Norway. All measurements were based on liquid chromatography tandem mass spectrometry. Briefly, for aTHF, THF, and THE, 100 µL of centrifuged urine was added to 228 µL of an enzyme-buffer cocktail (acetate buffer, 0.5 N, pH 5.1, with 7,500 units of β-glucuronidase type H-2 from *Helix pomatia* [Sigma-Aldrich, St. Louis, Missouri] and 5,000 units of β-glucuronidase from *Ampullaria* [Wako Pure Chemical Industries Ltd, Tokyo, Japan]). Samples were incubated at 55°C for 2 hours and fridge-centrifuged at 6000 × *g* for 20 minutes. Forty-four µL of supernatant was diluted 1:5 with 30:70 MeOH:H_2O (v/v) containing deuterated THF-d3 (5β-Pregnan-3α,11β,17α, 21-tetrol-20-one-9,11α,12-d_3, 95 atom % D) (C/D/N Isotopes Inc, Quebec, Canada) as the internal standard. After 20 minutes, equilibration samples were filtered through 0.45-µm filters. Chromatographic separation was performed on a Dionex 3000 ×2 Dual Analytical High-Performance Liquid Chromatography (HPLC) System (Dionex Corporation, Sunnyvale, California). Five µL was injected into a ZORBAX Eclipse XDB-C18 5-µm, 3.0 × 250 mm column (Agilent Technologies, Santa Clara, California). Mobile phase was 60:40 MeOH:H_2O with 0.1% formic acid. Flow rate was 500 µL/min, and column oven was set at 60°C. The mass spectrometric detector, an MDS Sciex API-4000 Q-Trap (Applied Biosystems, Carlsbad, California), operated with electrospray ionization (ESI) source in positive mode. Ion source conditions were as follows: curtain gas, 30 psig; collisionally activated dissociation (CAD), medium; ionspray voltage, 5,500 V; temperature, 350°C; gas 1, 50 psig; gas 2, 50 psig; entrance potential, 10 V; and resolution set to *unit*. The following multiple reaction monitoring (MRM) transitions were monitored: 349/313 and 349/99 (THF and aTHF), 347/149 and 347/91 (THE), and 352/316 and 352/92 (THF-d3). The between-day precision was below 7.4%, 9.9%, and 7.9% for THF, aTHF, and THE, respectively. Accuracy ranged from 94% to 115%.

For measurements of cortisol and cortisone in urine, 200 µL of urine was diluted 1:1 with the internal standard, deuterated cortisol-d4 (4-Pregnen-11β,17α,21-triol-3, 20-dione-9,11,12,12-d_4, 97.5 atom % D) (C/D/N Isotopes Inc, Quebec, Canada) in 1% formic acid. A 20-µL sample was injected into an Oasis hydrophilic-lipophilic–balanced (HLB) column, 2.1 × 20 mm, 25 µm (Waters Corporation, Milford, Massachusetts), for sample cleanup at a flow rate of 2,500 µL/min. Washing steps included 0.5 minute with 0.1% formic acid, 0.5 minute with 40:4:56 MeOH:NH_4OH:H_2O (v/v/v), and 1.0 minute with 0.1% formic acid. After 2.0 minutes, a valve directed the flow from a secondary pump through the extraction column in backflush mode and eluted retained substances to the analytic column (Sunfire 2.1 × 100 mm, 3.5 µm) (Waters Corporation, Milford, Massachusetts). This secondary pump was running a gradient from 10% to 50% acetonitrile with 0.1% formic acid from $t = 2$ to $t = 10$ minutes. Flow rate was 300 µL/min, and column temperature was 20°C. The API-4000 Q-Trap operated in ESI positive mode. Ion source conditions were as follows: curtain gas, 30 psig; CAD, medium; ionspray voltage, 5,500 V; temperature, 550°C; gas 1, 50 psig; gas 2, 50 psig; entrance potential, 10 V; and resolution set to *unit*. The between-day precisions were below 5.3% and 3.4% for cortisol and cortisone, respectively. Accuracy ranged from 99% to 108% for cortisol and from 88% to 100% for cortisone. There were no known interfering substances.

Indexes of Enzyme Activities

Activity of 11β-HSD (overall) was estimated with the (aTHF + THF)/THE index, and the activity of 11β-HSD2 was estimated with the UFF/UFE index.[10] Activities of 5α-reductase and 5β-reductase were calculated with

aTHF/UFF and THF/UFF indexes, respectively.[25] Subjects with 2 urinary samples (n = 10) had indexes computed from their mean values. To control for variation in urine concentration, urinary creatinine was measured using the Jaffé reaction (Cobas Integra analyzer, Roche Diagnostics GmbH, Mannheim, Germany) (urinary creatinine measure was missing for 4 subjects in the schizophrenia group and for 2 subjects in each of the bipolar disorder and healthy control groups).

Table 2. Median Urinary Free Cortisol, Urinary Free Cortisone, and Metabolites for Each Study Group

Substance	Bipolar Disorder (N = 69), Median (IQR)	Schizophrenia Spectrum Disorders (N = 87), Median (IQR)	Healthy Controls (N = 169), Median (IQR)	*P* Value
UFF, nmol/L	95.5 (140.1)	97.4 (115.8)	75.0 (126.0)	.37
UFE, nmol/L	238.0 (203.5)	237.0 (220.0)[a]	189.0 (183.0)	.041
THF, nmol/L	5,730.0 (10,085.0)[a]	6,720.0 (7,670.0)[b]	3,640.0 (5,670.0)	< .001
aTHF, nmol/L	5,100.0 (8,840.0)	7,060.0 (7,910.0)[b,c]	4,270.0 (6,590.0)	< .001
THE, nmol/L	9,275.0 (15,230.0)[a]	13,600.0 (14,270.0)[b]	6,800.0 (9,310.0)	< .001

[a] $P < .05$ vs healthy controls.
[b] $P < .001$ vs healthy controls.
[c] $P < .05$ vs bipolar disorder.
Abbreviations: aTHF = allo-tetrahydrocortisol, IQR = interquartile range, THE = tetrahydrocortisone, THF = tetrahydrocortisol, UFE = urinary free cortisone, UFF = urinary free cortisol.

Statistical Analysis

SPSS software version 15.0 (SPSS Inc, Chicago, Illinois) was used for the statistical analyses. Indexes of enzyme activities had skewed distribution and were logarithmically transformed for comparisons between groups with analysis of covariance. Included in the model as main effects were *group* (all patients, or schizophrenia and bipolar disorder, and healthy controls) and adjustments with backward elimination for age, gender, urinary creatinine, and time of sampling. We also tested the group × gender interaction. Effects of body mass index were added in a separate analysis, as this variable was available in a subset of the sample.

Analyses of the indexes were performed between the following medication groups: antipsychotics (n = 110) versus no antipsychotics (n = 43); mood stabilizers (n = 42) versus no mood stabilizers (n = 111); and the combination of antipsychotics and mood stabilizers (n = 24) versus no use of these types of medications (n = 25).

For testing between-group differences in UFF, UFE, aTHF, THF, THE, time of sampling, age, urinary creatinine, body mass index, and total scores for PANSS, IDS-C, and YMRS, we used the Kruskal-Wallis *H* test and/or the Mann-Whitney *U* test. Differences in gender were analyzed with the χ^2 test, and correlations were analyzed with the Spearman ρ. For all statistical analyses, the significance level was set at .05 (2-sided), and corrections of results were performed with the Bonferroni correction.

RESULTS

The uncorrected concentrations of UFF, UFE, and metabolites are shown in Table 2. There was a significant increase in UFE ($U = 11{,}153.5$; $Z = -2.4$; $P = .017$), aTHF ($U = 10{,}408.5$; $Z = -3.3$; $P = .001$), THF ($U = 9{,}406.5$; $Z = -4.5$; $P < .001$), and THE ($U = 9{,}270.5$; $Z = -4.5$; $P < .001$) in the combined patient group compared to healthy controls. Comparing the schizophrenia, bipolar disorder, and healthy control groups, significant between-group differences were found for UFE ($\chi^2_2 = 6.4$, $P = .041$), aTHF ($\chi^2_2 = 15.4$, $P < .001$), THF ($\chi^2_2 = 21.2$, $P < .001$), and THE ($\chi^2_2 = 23.8$, $P < .001$). These differences were due to increased concentrations in schizophrenia (UFE, $P = .014$; aTHF, $P < .001$; THF, $P < .001$; and THE, $P < .001$) and bipolar disorder (THF, $P = .010$; and THE, $P = .020$) compared to healthy controls. Allo-THF was increased in schizophrenia compared to bipolar disorder ($P = .043$); UFF did not differ significantly between groups (unadjusted).

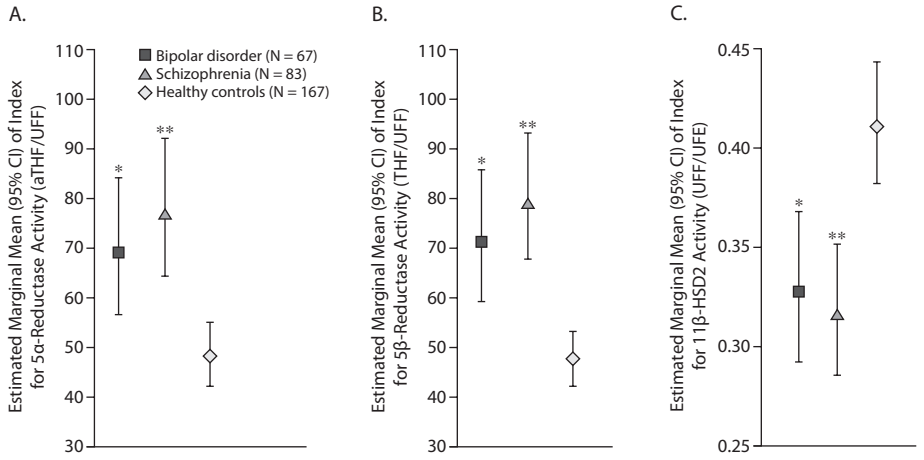
The cortisol metabolite indexes, estimating enzyme activities, were significantly different between the combined patient group and the healthy control group for 5α-reductase ($F_1 = 17.4$, $P < .001$), 5β-reductase ($F_1 = 27.0$, $P < .001$), and 11β-HSD2 ($F_1 = 18.2$, $P < .001$). Comparing the schizophrenia, bipolar disorder, and healthy control groups, significant between-group differences were found for 5α-reductase ($F_2 = 9.0$, $P < .001$), 5β-reductase ($F_2 = 13.9$, $P < .001$), and 11β-HSD2 ($F_2 = 9.2$, $P < .001$). Increased enzyme activity was present in both schizophrenia (5α-reductase, $P < .001$; 5β-reductase, $P < .001$; and 11β-HSD2, $P < .001$) and bipolar disorder (5α-reductase, $P = .016$; 5β-reductase, $P = .001$; and 11β-HSD2, $P = .007$) compared to healthy controls (Figure 1). There were no significant differences in enzyme activities between the bipolar disorder group and the schizophrenia group. All reported differences remained significant when including body mass index in the statistical model. Male subjects with schizophrenia tended to inactivate cortisol to a larger extent than male healthy controls, indicated by a group (bipolar disorder, schizophrenia, controls) × gender interaction for overall 11β-HSD, but this finding did not reach statistical significance ($P = .11$).

There were no significant differences in the enzyme indexes of cortisol metabolism between groups of medications. The enzyme indexes were not significantly correlated to total scores in PANSS, IDS-C, CDSS, or YMRS.

DISCUSSION

The present study demonstrates an increased systemic metabolism of cortisol in bipolar disorder and schizophrenia patients compared to healthy controls on the basis of findings of increased activities of the enzymes 5α-reductase, 5β-reductase, and 11β-HSD2. Enzyme activities in bipolar disorder and schizophrenia did not differ significantly. To the best of our knowledge, these are the first results to suggest that increased systemic metabolism of cortisol is related to the hyperactive HPA axis previously demonstrated in these disorders.[3,4]

Figure 1. Indexes of Enzyme Activities in Systemic Cortisol Metabolism[a]



[a]Estimated marginal means of indexes for (A) 5α-reductase, (B) 5β-reductase, and (C) 11β-HSD2 are presented. Indexes are significantly different between healthy controls and the bipolar disorder and schizophrenia spectrum groups. There are no significant differences in indexes comparing the bipolar disorder and schizophrenia spectrum groups.

*$P < .025$ vs healthy controls, **$P < .001$ vs healthy controls.

Abbreviations: 11β-HSD2 = 11β-hydroxysteroid dehydrogenase type 2, aTHF = allo-tetrahydrocortisol, THF = tetrahydrocortisol, UFE = urinary free cortisone, UFF = urinary free cortisol.

The enzyme indexes applied in the present study are widely accepted and used as estimates of systemic enzyme activities.[10,25] There are several reports[19,26] of index levels corresponding to concentrations of metabolites excreted in the urine, lending strongly to the suggestion that the present results reflect increased activity in cortisol-metabolizing enzymes in bipolar disorder and schizophrenia.

An increased systemic cortisol metabolism may lead to a dysfunctional HPA axis activity, as was suggested recently by transgene mediated delivery of hepatic 11β-HSD1 activity to 11β-HSD1 knockout mice.[14] The 11β-HSD1 knockout mice do not possess 11β-HSD1 in the brain, liver, or any other organ, with a resulting abruption of conversion of 11-dehydrocorticosterone (analogous to cortisone in humans) to corticosterone (cortisol in humans), an analog of increased metabolism of cortisol. In these mice, abnormalities in HPA axis activity, such as increased levels of corticosterone and adrenocorticotropic hormone[13,14] and decreased inhibition of corticosterone secretion after administration of exogenous cortisol,[13] are reported. However, normal activity was completely restored with transgene-mediated delivery of hepatic 11β-HSD1 activity,[14] indicating that altered systemic cortisol metabolism affects HPA axis functioning.

A series of studies[3,4,27–29] report dysfunctional HPA axes in bipolar disorder and schizophrenia; these findings parallel those in the 11β-HSD1 knockout mice. These results could be due to increased systemic cortisol metabolism, since raised basal levels of adrenocorticotropic hormone[27,29] and cortisol[28,29] (markers of HPA axis dysfunction) in bipolar disorder and schizophrenia correspond to findings in 11β-HSD1 knockout mice that seem to be reversed with the transgene-mediated delivery of hepatic 11β-HSD1 activity.[14] Analogous to the transgenic mouse model,[14] the indexes of enzyme activities in the present study relate to systemic cortisol metabolism (hepatic, renal).[10,25] Thus, the present findings suggest that an increased systemic cortisol metabolism is part of the pathophysiology of the HPA axis hyperactivity in bipolar disorder and schizophrenia. Further, it is possible to speculate that a higher turnover of cortisol renders the HPA axis more vulnerable to stress, affecting the course of mental illness. Interestingly, there is a case report of clinical improvement in a patient with schizophrenia treated with a 5α-reductase inhibitor.[30]

However, the exact mechanism of the HPA axis function and systemic cortisol metabolism interplay remains unclear. A compensatory increased HPA axis drive may follow an increased cortisol metabolism, as altered 5α-reductase and 5β-reductase activities affect the half-life of cortisol, and there is evidence that both 11β-HSD type 1 and type 2 modulate systemic cortisol level.[11,12] This compensatory mechanism is suggested in other disorders such as Alzheimer's disease[31] and polycystic ovary syndrome[32] and is also indicated in the transgenic mouse model.[14] In the present sample, the increase in metabolism could also be secondary to a primary increased HPA axis activity, with subsequent increase in metabolism to maintain equilibrium. However, this seems less likely as UFF levels, reflecting systemic, biologically active cortisol, did not differ significantly between the groups. There are several studies[12,15,33] of subjects with differing basal cortisol levels reporting no indications of enzyme induction on the basis of activity indexes. The stability of the metabolic activity is further supported by our findings of no correlations between the indexes and the symptom measurements. These findings support the concept that systemic metabolic activity is a trait marker in these mental disorders.

Studies of genetic factors related to different parts of the HPA axis have so far been unsuccessful in identifying

the causes of dysfunctions found in bipolar disorder and schizophrenia. In bipolar disorder, studies of glucocorticoid and corticotropin-releasing hormone receptors are basically negative[34,35]; studies of single-nucleotide polymorphisms (SNPs) of *FKBP5*, a gene coding for a product involved in glucocorticoid receptor function, yield contradicting results[36,37]; and no association is found with the corticotropin-releasing hormone gene.[38] In schizophrenia, there is 1 negative *FKBP5* study.[36] There is some evidence, though not uniform, for an association in both disorders with variants in the *YWHAH* gene, which codes for a protein (14-3-3η) blocking glucocorticoid receptor degradation.[39–41] Immune factors could also play a role in cortisol metabolism. Immune system abnormalities have been associated with schizophrenia and bipolar disorder,[42] immune-related risk genes were recently found in schizophrenia,[43] and immune mediators such as tumor necrosis factor (TNF)-α modulate the activity of 11β-HSD.[44] To the best of our knowledge, there have been no studies of genes specific for cortisol-metabolizing enzymes in mental disorders.

Cortisol metabolism has been found to be affected in various disorders, including obesity, metabolic syndrome, hypertension, polycystic ovary syndrome, apparent mineralocorticoid excess, and Alzheimer's disease.[10] Previous related studies in mental disorders include reports on post-traumatic stress disorder,[26,45] chronic fatigue syndrome,[46] eating disorders,[47] and depression.[15–19] Three of the 5 studies on depression found enzyme activities shifted toward reduced cortisol metabolism.[16,18,19] However, the mechanisms of HPA axis dysregulation may not be similar in depression and bipolar disorder/schizophrenia. The same direction of shift in enzyme activities in bipolar disorder and schizophrenia in this large sample strengthens the findings, as it is in accordance with the psychosis spectrum hypothesis of similar pathophysiology in bipolar disorder and schizophrenia.[1]

There are limitations to be aware of in the present study. Cross-sectional design does not allow for conclusions about the direction of the effects. There were between-group differences in age, gender, urinary creatinine, body mass index, and time of sampling, but these differences were adjusted for in the statistical model. Medication could also affect cortisol metabolism, but analyses showed no significant differences between groups based on types of medication taken versus not taken. Urine sampling for 24 hours would be preferable since it allows adjustment for effects of urine volume on UFF and UFE,[48] adjustment for diurnal variation, and analysis of absolute values of metabolite excretion. However, 24-hour urine collection would be difficult to implement in a mixture of inpatients and outpatients with psychosis spectrum disorders. A potential effect of volume and diurnal variation was adjusted for in the statistical analyses by including urinary creatinine and time of sampling as covariates.

To the best of our knowledge, this is the first study to show increased enzyme activities of systemic cortisol metabolism in bipolar disorder and schizophrenia in the direction of clearing cortisol. This finding indicates that systemic metabolism of cortisol may be an important factor in the pathophysiology and increased stress vulnerability of bipolar disorder and schizophrenia and provides further support for the HPA axis dysregulation hypothesis. Similar alterations in enzyme activities in bipolar disorder and schizophrenia are further in line with the psychosis continuum hypothesis. This novel finding related to the widely studied HPA axis should be explored further in terms of potential new drug targets, and it adds to the physiologic rationale for stress coping strategies in subjects with these disorders.

Author affiliations: Section for Psychosis Research, Clinic of Mental Health and Addiction, Oslo University Hospital, Oslo (Drs Steen, Larsson, Mork, Melle, and Andreassen); Acute Psychiatric Emergency Unit, Clinic of Mental Health and Addiction, Oslo University Hospital, Oslo (Drs Steen and Barrett); Institute of Medicine, University of Bergen, Bergen (Drs Methlie, Almås, and Løvås); Hormone Laboratory, Haukeland University Hospital, Bergen (Drs Methlie and Almås); Institute of Psychiatry, University of Oslo, Oslo (Drs Lorentzen, Hope, Larsson, Agartz, Melle, and Andreassen); Department of Research and Development, Clinic of Mental Health and Addiction, Oslo University Hospital, Oslo (Dr Lorentzen); Department of Psychiatry, Ostfold Hospital, Fredrikstad (Dr Hope); The National Centre for Suicide Research and Prevention, Institute of Psychiatry, University of Oslo, Oslo (Dr Mork); Department of Medicine, Haukeland University Hospital, Bergen (Dr Løvås); Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo (Dr Agartz); and Institute of Clinical Medicine, University of Oslo, Oslo, and Department of Medical Biochemistry and Hormone Laboratory, Oslo University Hospital, Oslo (Dr Berg), Norway.
Potential conflicts of interest: **Dr Andreassen** has received speakers bureau honoraria from AstraZeneca, GlaxoSmithKline, Bristol-Myers Squibb, and Janssen, but not for topics related to this article. **Drs Steen**, **Methlie**, **Lorentzen**, **Hope**, **Barrett**, **Larsson**, **Mork**, **Almås**, **Løvås**, **Agartz**, **Melle**, and **Berg** report no financial interests or personal affiliations relative to the content of this article.
Funding/support: The study was supported by an award from The Lundbeck Foundation, Lysaker, Norway; grants to the Thematically Organized Psychosis Research (TOP) study group from the University of Oslo, Oslo, Norway; Oslo University Hospital, Oslo, Norway; the Research Council of Norway, Oslo, Norway (#167153/V50, #163070/V50); and the South-Eastern Norway Regional Health Authority, Hamar, Norway (#2004-123, #2008-039).
Previous presentation: Presented as a poster at the 15th Biennial Winter Workshop in Psychoses; November 15–18, 2009; Barcelona, Spain; and at the 9th National Conference on Acute Psychiatry; February 18–19, 2010; Oslo, Norway.
Acknowledgments: The authors thank the patients and controls for participating in the study, and we thank the TOP study group members for contributing to data collection.

REFERENCES

1. Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses. *Schizophr Bull*. 2009;35(3):482–490.
2. Banki CM, Bissette G, Arato M, et al. CSF corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. *Am J Psychiatry*. 1987;144(7):873–877.
3. Lammers CH, Garcia-Borreguero D, Schmider J, et al. Combined dexamethasone/corticotropin-releasing hormone test in patients with schizophrenia and in normal controls, 2. *Biol Psychiatry*. 1995;38(12):803–807.
4. Watson S, Gallagher P, Ritchie JC, et al. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry*. 2004;184(6):496–502.
5. Goldstein JM, Seidman LJ, Makris N, et al. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biol Psychiatry*. 2007;61(8):935–945.
6. Young AH, Gallagher P, Watson S, et al. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology*. 2004;29(8):1538–1545.
7. Garner B, Berger GE, Nicolo JP, et al. Pituitary volume and early

treatment response in drug-naive first-episode psychosis patients. *Schizophr Res*. 2009;113(1):65–71.
8. Herman JP, Ostrander MM, Mueller NK, et al. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(8):1201–1213.
9. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression: hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am*. 1998;21(2):293–307.
10. Tomlinson JW, Stewart PM. Cortisol metabolism and the role of 11β-hydroxysteroid dehydrogenase. *Best Pract Res Clin Endocrinol Metab*. 2001;15(1):61–78.
11. Vogeser M, Gülberg V, Waggershauser T, et al. In-vivo quantification of hepatic 11β-hydroxysteroid dehydrogenase type I activity: a preliminary study. *Clin Biochem*. 2002;35(8):655–657.
12. Morita H, Isomura Y, Mune T, et al. Plasma cortisol and cortisone concentrations in normal subjects and patients with adrenocortical disorders. *Metabolism*. 2004;53(1):89–94.
13. Harris HJ, Kotelevtsev Y, Mullins JJ, et al. Intracellular regeneration of glucocorticoids by 11β-hydroxysteroid dehydrogenase (11β-HSD)-1 plays a key role in regulation of the hypothalamic-pituitary-adrenal axis: analysis of 11β-HSD-1-deficient mice. *Endocrinology*. 2001;142(1):114–120.
14. Paterson JM, Holmes MC, Kenyon CJ, et al. Liver-selective transgene rescue of hypothalamic-pituitary-adrenal axis dysfunction in 11β-hydroxysteroid dehydrogenase type 1-deficient mice. *Endocrinology*. 2007;148(3):961–966.
15. Raven PW, Taylor NF. Evidence for independent modulation of human 11-HSD and 5 α/5 β reductase activities. *Endocr Res*. 1996;22(4):811–815.
16. Raven PW, Taylor NF. 11β-HSD and 17β-HSD as biological markers of depression: sex differences and correlation with symptom severity. *Endocr Res*. 1998;24(3–4):659–662.
17. Weber B, Lewicka S, Deuschle M, et al. Increased diurnal plasma concentrations of cortisone in depressed patients. *J Clin Endocrinol Metab*. 2000;85(3):1133–1136.
18. Poór V, Juricskay S, Gáti A, et al. Urinary steroid metabolites and 11β-hydroxysteroid dehydrogenase activity in patients with unipolar recurrent major depression. *J Affect Disord*. 2004;81(1):55–59.
19. Römer B, Lewicka S, Kopf D, et al. Cortisol metabolism in depressed patients and healthy controls. *Neuroendocrinology*. 2009;90(3):301–306.
20. First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1995.
21. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996; 26(3):477–486.
22. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res*. 1990;3(4):247–251.
23. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
24. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
25. Ulick S, Tedde R, Wang JZ. Defective ring A reduction of cortisol as the major metabolic error in the syndrome of apparent mineralocorticoid excess. *J Clin Endocrinol Metab*. 1992;74(3):593–599.
26. Yehuda R, Bierer LM, Andrew R, et al. Enduring effects of severe developmental adversity, including nutritional deprivation, on cortisol metabolism in aging Holocaust survivors. *J Psychiatr Res*. 2009;43(9): 877–883.
27. Vieta E, Martínez-De-Osaba MJ, Colom F, et al. Enhanced corticotropin response to corticotropin-releasing hormone as a predictor of mania in euthymic bipolar patients. *Psychol Med*. 1999;29(4):971–978.
28. Cervantes P, Gelber S, Kin FN, et al. Circadian secretion of cortisol in bipolar disorder. *J Psychiatry Neurosci*. 2001;26(5):411–416.
29. Ryan MC, Sharifi N, Condren R, et al. Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. *Psychoneuroendocrinology*. 2004;29(8):1065–1070.
30. Koethe D, Bortolato M, Piomelli D, et al. Improvement of general symptoms in a chronic psychotic patient treated with finasteride: case report. *Pharmacopsychiatry*. 2008;41(3):115–116.
31. Rasmuson S, Andrew R, Näsman B, et al. Increased glucocorticoid production and altered cortisol metabolism in women with mild to moderate Alzheimer's disease. *Biol Psychiatry*. 2001;49(6):547–552.
32. Stewart PM, Shackleton CH, Beastall GH, et al. 5 α-reductase activity in polycystic ovary syndrome. *Lancet*. 1990;335(8687):431–433.
33. Morineau G, Boudi A, Barka A, et al. Radioimmunoassay of cortisone in serum, urine, and saliva to assess the status of the cortisol-cortisone shuttle. *Clin Chem*. 1997;43(8 Pt 1):1397–1407.
34. Moutsatsou P, Tsolakidou A, Trikkas G, et al. Glucocorticoid receptor alpha and beta isoforms are not mutated in bipolar affective disorder. *Mol Psychiatry*. 2000;5(2):196–202.
35. De Luca V, Tharmalingam S, Kennedy JL. Association study between the corticotropin-releasing hormone receptor 2 gene and suicidality in bipolar disorder. *Eur Psychiatry*. 2007;22(5):282–287.
36. Fallin MD, Lasseter VK, Avramopoulos D, et al. Bipolar I disorder and schizophrenia: a 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. *Am J Hum Genet*. 2005;77(6):918–936.
37. Willour VL, Chen H, Toolan J, et al; NIMH Genetics Initiative Bipolar Disorder Consortium. Family-based association of *FKBP5* in bipolar disorder. *Mol Psychiatry*. 2009;14(3):261–268.
38. Stratakis CA, Sarlis NJ, Berrettini WH, et al. Lack of linkage between the corticotropin-releasing hormone (CRH) gene and bipolar affective disorder. *Mol Psychiatry*. 1997;2(6):483–485.
39. Wong AH, Macciardi F, Klempan T, et al. Identification of candidate genes for psychosis in rat models, and possible association between schizophrenia and the 14-3-3η gene. *Mol Psychiatry*. 2003;8(2):156–166.
40. Duan S, Gao R, Xing Q, et al. A family-based association study of schizophrenia with polymorphisms at three candidate genes. *Neurosci Lett*. 2005; 379(1):32–36.
41. Grover D, Verma R, Goes FS, et al; NIMH Genetics Initiative Bipolar Disorder Collaborative, Bipolar Disorder Phenome Group. Family-based association of *YWHAH* in psychotic bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(7):977–983.
42. Hope S, Melle I, Aukrust P, et al. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. *Bipolar Disord*. 2009;11(7): 726–734.
43. Stefansson H, Ophoff RA, Steinberg S, et al; Genetic Risk and Outcome in Psychosis (GROUP). Common variants conferring risk of schizophrenia. *Nature*. 2009;460(7256):744–747.
44. Ignatova ID, Kostadinova RM, Goldring CE, et al. Tumor necrosis factor-α upregulates 11β-hydroxysteroid dehydrogenase type 1 expression by CCAAT/enhancer binding protein-β in HepG2 cells. *Am J Physiol Endocrinol Metab*. 2009;296(2):E367–E377.
45. Yehuda R, Bierer LM, Sarapas C, et al. Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001. *Psychoneuroendocrinology*. 2009;34(9):1304–1313.
46. Jerjes WK, Peters TJ, Taylor NF, et al. Diurnal excretion of urinary cortisol, cortisone, and cortisol metabolites in chronic fatigue syndrome. *J Psychosom Res*. 2006;60(2):145–153.
47. Poór V, Bufa A, Bíró I, et al. Urinary steroid measurements in some endocrine and psychiatric diseases. *Curr Med Chem*. 2005;12(11):1339–1342.
48. Fenske M. Urinary free cortisol and cortisone excretion in healthy individuals: influence of water loading. *Steroids*. 2006;71(11-12):1014–1018.

 © Copyright 2011 Physicians Postgraduate Press, Inc.