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SRD5A2 is associated with increased cortisol metabolism in schizophrenia spectrum disorders

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ABSTRACT

Objective: Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is documented in bipolar disorder and schizophrenia, but the mechanism is unclear; recently, increased activity of cortisol metabolizing enzymes was indicated in these disorders. We investigated whether five genes involved in cortisol metabolism were associated with altered activity of cortisol metabolizing enzymes in bipolar disorder (BD) and schizophrenia spectrum disorders (SCZ).

Methods: A case–control sample of subjects with BD (N = 213), SCZ (N = 274) and healthy controls (N = 370) from Oslo, Norway, were included and genotyped from 2003 to 2008. A sub-sample (healthy controls: N = 151; SCZ: N = 40; BD: N = 39) had estimated enzyme activities based on measurements of urinary free cortisol, urinary free cortisone and metabolites. A total of 102 single nucleotide polymorphisms (SNPs) in the *SRD5A1*, *SRD5A2*, *AKR1D1*, *HSD11B1* and *HSD11B2* genes were genotyped, and significant SNPs analyzed in the sub-sample.

Results: There was a significant association of rs6732223 in *SRD5A2* (5α-reductase) with SCZ ($p = 0.0043$, Bonferroni corrected $p = 0.030$, T risk allele). There was a significantly increased 5α-reductase activity associated with rs6732223 (T allele) within the SCZ group ($p = 0.011$).

Conclusions: The present data suggest an interaction between SCZ and *SRD5A2* variants coding for the enzyme 5α-reductase, giving rise to increased 5α-reductase activity in SCZ. The findings may have implications for cortisol metabolizing enzymes as possible drug targets.

Abbreviations: ACTH, adrenocorticotrophic hormone; aTHF, allo-tetrahydrocortisol; BD, bipolar disorder; BMI, body mass index; CDSS, Calgary Depression Scale for Schizophrenia; CHISQ, Chi-squared statistic; CRH, corticotrophin releasing hormone; DF, degrees of freedom; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; HWD, Hardy–Weinberg disequilibrium; IDS-C, Inventory of Depressive Symptoms; LD, linkage disequilibrium; MAF, minor allele frequency; PANSS, Positive and Negative Syndrome Scale; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCID 1, The Structured Clinical Interview for DSM-IV Axis I Disorders; SCZ, schizophrenia (spectrum); SNP, single-nucleotide polymorphism; THE, tetrahydrocortisone; THF, tetrahydrocortisol; TOP, Thematically Organized Psychosis; UFE, urinary free cortisone; UFF, urinary free cortisol; YMRS, Young Mania Rating Scale.

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1. Introduction

Bipolar disorder (BD) and schizophrenia (SCZ) are severe mental disorders with lifetime prevalences of 1–2% (Merikangas et al., 2007; Perala et al., 2007). They cause severe individual disability as well as a major economical burden to the society (Kleinman et al., 2003; Mangalore and Knapp, 2007). BD and SCZ spectrum disorders are considered part of a common psychosis spectrum, sharing both etiological components and symptom patterns (Craddock et al., 2009). The combination of several gene variants, each conferring a minor risk, probably adds up to a high heritability with estimates of 80% (Cichon et al., 2009). Several candidate genes have been suggested (Barnett and Smoller, 2009; Owen et al., 2009), but the genetic and environmental causes and pathophysiological mechanisms remain largely unknown.

The hypothalamic-pituitary-adrenal (HPA) axis is an important response system for both physical and mental stressors (Biondi and Picardi, 1999), and a well described biological correlate for the stress-vulnerability hypothesis of several mental disorders (de Kloet, 2008). In general, the hypothalamus receives both stimulatory and inhibitory signals originating from the limbic system, regulating corticotrophin releasing hormone (CRH). CRH stimulates adrenocorticotrophic hormone (ACTH) from the anterior pituitary, and ACTH acts on the adrenal cortex for cortisol secretion. Cortisol has regulatory negative feedback effects on the axis (Herman et al., 2005). Limbic abnormalities and dysfunction of the axis are well documented in BD (Blumberg et al., 2003; Daban et al., 2005) and SCZ (Ebdrup et al., 2010; Walker et al., 2008). On the basis of findings including abnormal activity in euthymia (Watson et al., 2004) and in close relatives (Mondelli et al., 2008), it has been argued that the HPA axis is involved in the pathophysiology of these disorders. Several trials with drugs targeting the HPA axis have been initiated and with some promising results (Gallagher et al., 2008; Marco et al., 2002; Young et al., 2004). However, despite extensive research, the pathophysiology underlying the dysfunction is still unclear.

The genetics of the HPA axis in BD and SCZ has been explored, but not with uniform results. Studies of genes coding for CRH (Stratakis et al., 1997), the CRH receptor (De Luca et al., 2007) and the glucocorticoid receptor (GR) (Moutsatsou et al., 2000) are generally negative in BD. Studies of the FK506 binding protein 5 gene, a gene involved in GR functioning, are negative in SCZ (Fallin et al., 2005) and inconclusive in BD (Fallin et al., 2005; Willour et al., 2009). However, there are indications that both disorders are associated with variants of the 14-3-3 eta chain gene (Duan et al., 2005; Grover et al., 2009; Wong et al., 2003) which is involved in GR turnover.

Recently we found increased systemic activity of cortisol metabolizing enzymes (5α-reductase, 5β-reductases and 11β-hydroxysteroid dehydrogenase type 2 [11β-HSD2]) in BD and SCZ (Steen et al., in press). This was the first time that abnormal metabolism of cortisol was implicated as a potential factor underlying the HPA axis pathology in these disorders. However, studies on other mental disorders including chronic fatigue syndrome (Jerjes et al., 2006), posttraumatic stress syndrome (Yehuda et al., 2009a, b), eating disorders (Poor et al., 2005) and depression (Poor et al., 2004; Raven and Taylor, 1996; Raven and Taylor, 1998; Romer et al., 2009; Weber et al., 2000) have previously addressed the issue of cortisol metabolism. Cortisol metabolism has also been subject to interest in various somatic disorders including obesity (Andrew et al., 1998) and metabolic syndrome (Anagnostis et al., 2009), conditions associated with BD and SCZ (Birkenaes et al., 2007). The findings of increased systemic cortisol metabolism in BD and SCZ, together with several reports of the metabolism influencing HPA axis functioning (Paterson et al., 2007; Rasmuson et al., 2001; Stewart et al., 1990), suggest cortisol metabolism as a part in the mechanism of the HPA axis dysfunction. This indicates that abnormal cortisol metabolism is linked to the pathophysiology of these disorders. To the best of our knowledge there are not yet any studies on candidate genes coding for enzymes in the cortisol metabolism in BD and SCZ.

Our objective in the present study was to investigate if variations in genes coding for cortisol metabolizing enzymes could explain the findings of increased activity in these enzymes in BD and SCZ (Steen et al., in press). Our specific aims to investigate were 1) if the distribution of single-nucleotide polymorphism (SNP) genotypes in genes coding for 5α-reductase, 5β-reductases, 11β-HSD1 and 11β-HSD2 in BD, SCZ and healthy control groups indicated SNPs for analyses with enzyme data; 2) if SNPs suggested in 1) were associated with an altered enzyme activity; and 3) if the combination of diagnosis and SNPs in genes coding for 5α-reductase, 5β-reductases, 11β-HSD1 and 11β-HSD2 were associated with an altered enzyme activity. These aims were approached combining genetic data with a reanalysis of our enzyme data (Steen et al., in press).

2. Methods

2.1. Subjects

The study is based on the case–control sample of the ongoing Thematically Organized Psychosis (TOP) Study that is carried out by the University Hospitals of Oslo, Norway. Subjects were included and genotyped from 2003 to 2008, and constitute a total sample of 213 patients with BD, 274 patients with SCZ and 370 healthy controls. Characteristics of the sample are presented in Table 1.

Patients were included according to the following criteria: Caucasian ethnicity; being registered as in- or out-patients in the psychiatric services of any one of the four hospitals in Oslo; age 18 to 65 years; meeting DSM-IV criteria for schizophrenia spectrum disorders (schizophrenia, schizophreniform and schizoaffective disorder), in the following termed "schizophrenia (SCZ)", or bipolar disorder (bipolar I disorder, bipolar II disorder and bipolar disorder not otherwise specified), in the following termed "bipolar disorder (BD)"; and being willing and able to give written, informed consent of participation. Exclusion criteria were: history of moderate or severe head injury and neurological disorders. Inclusion and diagnostic interviews were done by trained clinical research personnel using The Structured Clinical Interview for DSM-IV Axis I Disorders, SCID 1 (First et al., 1995). Inter-rater reliability was good, with an overall kappa score of 0.77 (95% C.I: 0.60–0.94). For more details, see (Steen et al., in press).

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. The healthy control group was screened, including the use of Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994), to ensure that the subjects or any of their close relatives did not have a lifetime history of a severe psychiatric disorder.

About 90% of the patients and 85% of controls had both of their parents born in Norway, while the rest had one parent from another

Table 1
Sample characteristics of genotyped subjects.

	BD (N = 213)		SCZ (N = 274)		HC (N = 370)		Sum (N = 857)	
	N	%	N	%	N	%	N	%
Males	85	40	151	55	189	51	425	50
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)[a]	41.1	12.4	38.1	10.8	39.2	10.3	39.3	11.0

BD = bipolar disorder; SCZ = schizophrenia spectrum; HC = healthy controls; N = number; SD = standard deviation.
[a] Mean age in 2010.