



Associations between common arginine vasopressin 1b receptor and glucocorticoid receptor gene variants and HPA axis responses to psychosocial stress in a child psychiatric population

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ABSTRACT

On the one hand, a suitable response to daily stressors is crucial for adequate functioning in any natural environment. On the other hand, depending on the individual's genetic makeup, prolonged stress that is accompanied by an inappropriate level of responsiveness may lead to physiological and psychiatric disorders. Several psychiatric conditions have been linked with stress and alterations in hypothalamic–pituitary–adrenal (HPA) activity. While stress is a general phenomenon, illness is only seen in a proportion of individuals, suggesting that genetic factors may play a role in the ability to cope with stress. In children, relatively little research has been conducted to determine the impact of genetic factors on the variability in HPA axis functioning. In the present exploratory investigation, 106 prepubertal children were studied to estimate the impact of four glucocorticoid receptor gene (*NR3C1*) polymorphisms (*NR3C1*-1 [rs10482605], *ER22/23EK* [rs6190], *N363S* [rs6195], *N766N* [rs6196]) and five arginine vasopressin (AVP) receptor 1b gene (*AVPR1b*) polymorphisms (*AVPR1b_s1* [rs28536160], *AVPR1b_s2* [rs28373064], *AVPR1b_s3* [rs33976516], *AVPR1b_s4* [rs33985287], *AVPR1b_s5* [rs33933482]) on cortisol responses after a psychosocial stress test (public speaking task). *ER22/23EK* carriers had significantly lower cortisol responses to psychosocial stress compared with noncarriers. These findings provide evidence for the relevance of the *ER22/23EK* polymorphism in childhood HPA axis regulation. However, the small number of *ER22/23EK* subjects does not allow us to draw definitive conclusions about the genotypic effect.

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1. Introduction

Recent studies in clinical and developmental neuroscience show an increased interest in understanding the relevance of the hypothalamic–pituitary–adrenal (HPA) axis in child and adolescent psychiatry. The HPA axis is involved in neuroendocrine and behavioural responses to stress affected by developmental influences (Lupien et al., 2000; Meaney, 2001). Besides the well-documented influences of early developmental processes on these neurobehavioural systems of stress, there is also evidence that childhood is a time of plasticity in HPA axis functioning. Several studies have provided evidence for an association between HPA axis functioning and psychiatric problems (Kirschbaum

and Hellhammer, 1994; Chrousos, 1997; Levine, 2000; Preussner et al., 2003). Research on this topic is based on the role of the HPA axis in stress regulation. In stressful situations, the hypothalamus secretes corticotropin-releasing hormone (CRH), which, in synergy with arginine vasopressin (AVP), stimulates the pituitary gland to secrete adrenocorticotrophic hormone (ACTH). Subsequently, ACTH is released, which causes the adrenal glands to produce cortisol. Changes in cortisol concentrations influence immunity, metabolism, growth, reproduction and other important physiological processes (Chrousos, 1997; Sapolsky et al., 2000; De Kloet, 2003).

HPA axis functioning has not only been studied in the context of immediate stress, but also in psychiatric problems that are associated with severe or chronic stress. Abnormal responses to stress have been reported in child and adolescent psychiatry. For example, there is evidence for altered HPA axis functioning in children and adolescents with dysthymia (Gispens-de Wied et al., 1998; Jansen et al., 1999), depression (Casat and Powell, 1988; Dahl et al., 1992; Luby et al.,

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Table 1
Demographic characteristics of patients and healthy controls.

Measure	ADHD-C (n = 51)		ADHD-I (n = 12)		SP (n = 18)		CONTROL (n = 25)		P
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Age	8.52	1.84	8.70	1.61	9.29	0.82	8.71	1.41	0.377
Gender*	43/8		10/2		9/9		14/11		0.007
Tanner	1.05	0.12	1.09	0.26	1.12	0.26	1.09	0.24	0.582
BMI	16.32	2.00	16.41	1.89	16.59	1.13	16.78	1.62	0.754
SES	39.52	7.45	43.66	7.13	46.09	4.66	44.61	4.89	0.052
TIQ	99.72	8.23	101.92	10.03	105.17	7.46	102.44	9.44	0.131
VIQ	100.52	9.79	102.04	10.02	104.02	7.33	103.38	13.12	0.541
PIQ	99.12	7.79	101.99	9.84	105.38	7.09	101.73	10.41	0.066

Mean values and standard deviations.

Note: * Male/female ratio, BMI=Body Mass Index, SES=Socioeconomic status, TIQ=Total Intelligence Quotient, VIQ=Verbal Intelligence Quotient, PIQ=Performance Intelligence Quotient; ADHD-C=Attention deficit hyperactivity disorder, combined subtype; ADHD-I=predominantly inattentive subtype; SP=Social phobia.

2003), posttraumatic stress disorder (PTSD) (Goenjian et al., 1996, 2003; Kaufman et al., 1997a; Duval et al., 2004), attention-deficit/hyperactivity disorder (ADHD) (King et al., 1998; Hong et al., 2003; Yang et al., 2007; Blomqvist et al., 2007), anxiety disorders (Granger et al., 1994; Martel et al., 1999; Gerra et al., 2000; Coplan et al., 2002; Dorn et al., 2003; Terleph et al., 2006; van West et al., 2008), pervasive developmental disorder, autism and multiple complex developmental disorder (Jansen et al., 1999, 2000, 2003; Corbett et al., 2006; Marinovic-Curin et al., 2008), and oppositional-defiant disorder (ODD) and conduct disorder (CD) (Gispens-de Wied et al., 1998; Van Goozen et al., 1998, 2000; Snoek et al., 2004; Van de Wiel et al., 2004; McBurnett et al., 2005; Popma et al., 2006).

The various functions of the HPA axis are largely determined by well-regulated gene expression in tissues at different levels of the axis. The sophisticated use of molecular biology techniques has allowed molecular cloning of a number of genes encoding hormones or secretory proteins.

For a number of HPA axis functional candidate genes, our research group developed single-nucleotide polymorphism (SNP) maps and studied them in a haplotype-based association approach in samples of patients with affective disorders. We have studied in detail so far four genes coding for the CRH receptor 2 (CRHR2) (Villafuerte et al., 2002), the CRH binding protein (CRH-BP) (Claes et al., 2003; Van den Eede et al., 2007a,b), the AVP receptor 1B (AVPR1B) (van West et al., 2004) and the glucocorticoid receptor (NR3C1) (van West et al., 2006). An interesting finding was a protective effect of a major haplotype of AVPR1B for major depression in a Belgian and a Swedish sample (van West et al., 2004). Further, we showed that polymorphisms in the 5' region of NR3C1 – most probably promoter polymorphisms – play a role in the genetic vulnerability for major depression, again in a Belgian and a Swedish sample with recurrent major depression (van West et al., 2006). In the Swedish sample, the rare allele of SNP ER22/23EK was overrepresented in patients, a finding that was subsequently confirmed in an independent study in German patients (Van Rossum et al., 2006). In the Belgian sample, the association was mainly driven by SNP NR3C1-1 (rs10482605), a polymorphism with a functional effect on GR gene expression (Wüst, 2007).

The 80-kb-large NR3C1 is located on chromosome 5q31–q32. The gene comprises nine exons (Nobukuni et al., 1995). Exon 1 and part of exon 2 contain the 5'UTR, exons 2–9 the coding sequences, and part of exon 9 the 3'untranslated region (UTR) (Nobukuni et al., 1995). Recently, two additional alternative first exons (designated exons 1A and 1B) were identified upstream of exon 1 (now exon 1C) (Breslin et al., 2001). At least three promoters regulate the transcriptional activity of NR3C1 (Breslin et al., 2001). The 12-kb-large gene encoding AVPR1b is located on human chromosome 1q32 and consists of two exons that code a 424-amino acid sequence.

If it is true that GR and AVPR1b polymorphisms increase the vulnerability for major depression, it is logical to assume that these SNPs alter the stress response. To test this hypothesis, the present study was conducted to estimate the impact of these four NR3C1 and five AVPR1b polymorphisms on cortisol responses to psychosocial stress in a child psychiatric population.

2. Methods

2.1. Subjects

The research sample consisted of 106 prepubertal children (51 children with attention deficit hyperactivity disorder, combined subtype [ADHD-C], 12 children with ADHD, predominantly inattentive subtype [ADHD-I], 18 children with social phobia (SP), and 25 healthy controls) who all underwent a psychosocial stress test (cfr. infra). Demographic variables are shown in Table 1.

All patients were recruited from the psychiatric outpatients clinic, at the University Center of Child and Adolescent Psychiatry in Antwerp. Parent ratings of behaviour were ascertained using the Child Behavior Checklist (CBCL) (Achenbach, 1991a). Teacher ratings of behaviour were obtained using the Teacher Report Form (TRF) (Achenbach, 1991b). All patients were diagnosed by a semistructured interview: the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version 1.0 with supplement (K-SADS-PL) (Kaufman et al., 1997b) for all ADHD children and the Anxiety Disorders Interview Schedule for DSM-IV: Child and Parent Versions (ADIS-IV-C/P) (Siebelinck and Treffers, 2001; Silverman and Albano, 1996) for children with SP. Diagnoses were made according to the DSM-IV-TR (APA, 2000) by a trained child psychiatrist. All subjects were medication-naïve. Twenty-five control subjects between 6 and 12 years old were recruited from grades 1 to 6 of regular local elementary schools and screened for psychiatric problems, using the CBCL filled out by the parents. None of the children had any symptom cluster score above the 98th percentile. All patients and control individuals had parents of Belgian nationality.

All children with a Full Scale IQ, as measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974) of less than 85 and children with a history of any neurologic or endocrinologic disorder and steroid medication were excluded from this study. Stage of pubertal development was assessed in the parent interview using schematic drawings of secondary sex characteristics associated with the five standard Tanner stages of pubertal development (score range: 1–5) (Marshall and Tanner, 1969). Subjects with a score higher than 2 were excluded from the study. As a second measure of physical development, the body mass index (BMI) was computed. Socioeconomic status (SES) was measured using the Hollingshead Four-Factor Index of Social Status (Hollingshead, 1975). This measure generates an SES score for each family based upon maternal and paternal education and occupation.

The Medical Ethical Committee of the University of Antwerp approved the research project, and parents gave written informed consent after the purpose and course of the study had been explained.

2.2. Experimental procedure and saliva sampling

The psychosocial stress test consisted of a public speaking task (PST), which has been proved to be an effective stressor in both children and adults (Dickerson and Kemeny, 2004; Kudielka et al., 2004). The PST was embedded in a 135-min test session, consisting of an initial resting period (60 min), the PST (15 min) and a post-test resting period (60 min) (Table 2). For this population, we used an adapted version of the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), primarily by shortening its duration and increasing its relevance to participants. This procedure has been described in detail elsewhere (van West et al., 2008).

For each subject, seven saliva samples were collected for measurement of the cortisol concentration. The first saliva sample was taken during the initial resting period, 30 min after the start of the test session ($t = -30$). The second sample was taken after 60 min, at the end of the initial rest period just before the public speaking task (T0). Saliva was also collected right after the 10-min preparation period (T10) and after the 5-min talk (T15). During the second 1-h rest period, a further three saliva samples were collected at 20-min intervals (T35, T55, T75) (Table 2). As a specific measure of responsivity to the stressor, the following cortisol variables were computed:

Table 2
Study design.

Time	Prestress (60 min)		Stress (15 min)			Poststress (60 min)		
	-60	-30	0	10	15	35	55	75
Task	Q	Q	Introduction Preparation	PST	Judgement	Q	Game	Game
Cortisol		Cort1	Cort2	Cort3	Cort4	Cort5	Cort6	Cort7

Time schedule of the psychosocial stress test. (Q: Questionnaires; Cort: cortisol).

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