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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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 adrenocorticotropic 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 (Gispen-de Wied et al., 1998; Jansen et al., 1999), depression (Casat and Powell, 1988; Dahl et al., 1992; Luby et al., 2000). Stress-induced changes in HPA axis functioning can have a significant influence on the maintenance of psychiatric conditions.
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; Terlep 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) (Gispen-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.
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