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Corticotropin (ACTH)-reactive immunoglobulins in adolescents in relation to antisocial behavior and stress-induced cortisol response. The TRAILS study

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Summary Elevated levels of corticotropin (ACTH)-reactive immunoglobulins (ACTH IgG) were found in males with conduct disorder, suggesting their involvement in the biology of antisocial behavior. We first aimed to confirm these findings in a large general population sample of adolescents. Secondly, we studied the association between ACTH IgG levels and hypothalamic—pituitary—adrenal (HPA) axis response to stress.

Free and total ACTH IgG levels were measured in sera of 1230 adolescents (15—18 years). HPA axis activity was determined by measuring salivary cortisol before, during, and after a social stress test. Antisocial behavior was assessed using the Antisocial Behavior Questionnaire. ACTH peptide and IgG affinity kinetics for ACTH were assayed in a subsample of 90 adolescents selected for high or low ACTH IgG levels.

In boys, higher total ACTH IgG levels were associated with higher antisocial behavior scores ($\beta = 1.05$, $p = 0.04$), especially at high levels of free ACTH IgG. In girls, antisocial behavior was associated with low free ACTH IgG levels ($\beta = -0.20$, $p = 0.04$). Stress-induced cortisol release was associated with free ACTH IgG in boys ($\beta_{\text{area under the curve}} = -0.67$, $p < 0.01$), and with total

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ACTH IgG in girls ($\beta_{recovery} = 0.84$, $p = 0.05$). The affinity kinetics assay showed that ACTH IgG association rates were lower in both boys and girls with high ACTH IgG levels.

These data show that ACTH IgG levels are related to antisocial behavior and HPA axis response to stress in adolescents. The mechanisms behind these associations, including different ACTH binding properties of IgG in subjects with antisocial behavior, deserve further attention.

1. Introduction

Antisocial behavior often develops during childhood and adolescence and can manifest itself in delinquency. Research into neurobiological mechanisms involved in antisocial behavior has focused on the hypothalamic—pituitary—adrenal (HPA) axis, an important regulator of the physiological stress response. Its dysgregulation has been linked to externalizing problems (van Goozen et al., 2007; Alink et al., 2008; Ruttle et al., 2011). While some studies have reported associations of aggression and antisocial behavior with low cortisol levels (McBurnett et al., 2000; Shoal et al., 2003; Poustka et al., 2010; Haltigan et al., 2011), others have found no association (Klimes-Dougan et al., 2001), or higher cortisol levels in adolescents with externalizing behavior problems (McBurnett et al., 2005; van Bokhoven et al., 2005). The inconsistent findings and weak associations between cortisol and antisocial behavior increase the need for investigating other factors of HPA axis functioning that could influence antisocial behavior. Corticotropin (ACTH)-reactive immunoglobulins (IgG) are one such factor to explore.

High levels of ACTH IgG were found in prisoners and males with conduct disorder (Fetissov et al., 2006), suggesting their association with antisocial behavior, maybe through interfering with the HPA axis and altering stress-related behavior. It is plausible that ACTH IgG influence cortisol release upon stress by modulating ACTH action. This in turn could result in stress-induced behavior changes like impulsivity and aggression (Haller and Kruk, 2006). A similar model has previously been proposed for IgG against α-MSH, an ACTH-derived peptide (Sinno et al., 2009). According to this model, neuropeptide-reactive IgG may play a role in peptide transportation, protecting peptides from degradation by peptidases. An increase in affinity of such IgG would result in neutralization, decreasing peptide transportation and biological activity (Sinno et al., 2009). Both unbound ('free') IgG and IgG in immune complexes circulate in the blood. To be able to distinguish between the roles of free and total IgG, it may be informative to look at both pools separately (Gustaw et al., 2008; Deloumeau et al., 2010).

The previous study of ACTH IgG and antisocial behavior included males with severe conduct problems ($n = 20$), prisoners ($n = 20$), and healthy volunteers ($n = 22$) (Fetissov et al., 2006). It was the first study to demonstrate elevated ACTH IgG levels in aggressive and violent subjects compared to healthy controls. In this study, antisocial behavior of the controls was not measured and likely the prisoners were at the extreme end of the antisocial behavior spectrum. The study could not adjust for potential covariates (e.g. age, socioeconomic status). Our study is the first to investigate associations between ACTH IgG and both antisocial behavior and HPA axis response in a large sample of adolescents from the general population, making it possible to adjust for covariates. Most studies on antisocial behavior and low cortisol levels have focused on males (McBurnett et al., 2000; Shoal et al., 2003; Popma et al., 2006; Poustka et al., 2010), but a similar pattern has been reported in girls (Pajer et al., 2001). Both HPA axis and the immune system are differentially regulated in males and females (Gaillard and Spinedi, 1998). Knowing this, we were interested in exploring sex differences in our study.

Thus, the aim of this study was to validate the finding that ACTH IgG levels are associated with antisocial behavior in a large sample of male adolescents, and to investigate if such associations could also be found in females. Furthermore, we hypothesized that ACTH IgG are associated with HPA axis activity. We tested this by linking serum ACTH IgG levels to cortisol responses during a social stress test. We further characterized ACTH IgG properties by studying their affinity kinetics in adolescents with high or low ACTH IgG levels.

2. Methods

2.1. Participants

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a cohort study that follows young adolescents (10—12 years) into adulthood (Huisman et al., 2008). The study was approved by the National Dutch Medical Ethics Committee. Informed consent was required for participation, for each assessment separately. Measurements, consisting of validated questionnaires, interviews and biological measures, are taken every 2—3 years. The first assessment wave ran from March 2001 to July 2002 (T1). During T1, 2230 children were enrolled (response rate 76.0%; de Winter et al., 2005), of whom 1816 (81.4%) participated in T3 (September 2005—December 2007). During T3, 744 adolescents were invited to perform a series of laboratory tasks (experimental session) on top of the usual assessments, of whom 715 (96.1%) agreed to do so. The costly and labor-intensive nature of the laboratory tasks precluded assessing the whole sample. Adolescents with a higher risk of mental health problems had a greater chance of being selected for the experimental session. High risk was defined based on T1 measures of temperament (high frustration and fearfulness, low effortful control), lifetime parental psychopathology, and living in a single-parent family. In total 66.0% of the focus sample had at least one of the above described risk factors; the remaining 34.0% were selected randomly from the low-risk TRAILS participants. The focus sample still represented the whole range of problems seen in a normal population of adolescents. The present study focused on data from T3 (15—18 years). Blood serum was available from 1230 participants (573 boys). Of these participants, 590 (286 boys) took part in the experimental session, including the Groningen Social Stress Test (GSST),