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Effect of α_{2A}-adrenoceptor C-1291G genotype and maltreatment on hyperactivity and inattention in adolescents

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ABSTRACT

The C-1291G polymorphism (rs1800544) in the promoter region of the α_{2A}-adrenoceptor gene (ADRA2A) has been associated with attention deficit and hyperactivity in clinical samples. We have examined the effect of ADRA2A C-1291G on inattentive, hyperactive and aggressive behaviour in a population representative cohort of healthy schoolchildren, and possible interaction of genotype with family relations. Ratings on aggressiveness, motor restlessness and concentration difficulties were obtained from the class teachers by using the Hyperactivity Scale of af Klinteberg, and the teacher-report version of SNAP-IV. The relations in the family were reported by children. Symptom scores, self-reports and genotype data of 429 15-years old children (196 boys, 233 girls) were available for analysis. There was a significant interaction effect of maltreatment and the ADRA2A genotype on behavioural functioning in 15 years old boys. Boys with CC genotype and higher score of maltreatment demonstrated more overactive behaviour and concentration difficulties than boys with CC genotype and low maltreatment score. They also had more inattentive symptoms measured by SNAP-IV. Among boys with low maltreatment score, subjects with CC genotype demonstrated less overactivity than G allele carriers. In girls, the G allele carriers did not differ from the CC genotype, but in maltreated girls with GG genotype aggression and inattention symptoms were reduced, and the score of aggressive behaviour was also lower compared to maltreated girls with CC genotype. Our data suggest that family environmental factors may act together with the α_{2A}-adrenoceptor genotype to increase the expression of hyperactive and inattentive symptoms in adolescents.

1. Introduction

The noradrenergic projections ascending from the locus coeruleus act as a central arousal system and have been implicated in vigilance, memory, irritability, and hostility. Several authors have emphasised the role of noradrenaline in human inattentive and hyperactive behaviour (Halperin et al., 1997; Biederman and Spencer, 1999). Activation of presynaptic and somatodendritic α_{2A} adrenoceptors inhibits noradrenaline release and firing of noradrenergic neurons (Starke, 2001). Moreover, the α_{2A} adrenoceptors modulate release of other major neurotransmitters such as serotonin and dopamine (Scheibner et al., 2001). The core pathology of attention deficit/hyperactivity disorder (ADHD) is hypothesised to include α_{2A}-adrenergic receptor activity dependent network involving the prefrontal cortex and locus coeruleus (Arnsten and Li, 2005). Therefore alterations in a α_{2A} receptor expression or function may produce deficits in inhibitory control and the gene for α_{2A} receptor is an attractive candidate for ADHD studies.

The α_{2A}-adrenoceptor gene (ADRA2A) is located in chromosome 10q24-26. An MspI restriction site polymorphism (rs1800544) in the promoter region of the gene, originated by a transversion C to G at position −1291, was identified by Lario et al. (1997). Association studies of this ADRA2A MspI polymorphism in families with ADHD proband using a transmission disequilibrium test analysis have yielded both positive (Park et al., 2005) and negative results (Xu et al., 2001; Roman et al., 2003; Wang et al., 2006). However, previous investigations have demonstrated that the C-1291G polymorphism of ADRA2A is associated with the severity of ADHD symptoms in clinical samples. Among ADHD patients, subjects with the GG genotype have more often inattentive and combined symptoms (Roman et al., 2003; Schmitz et al., 2006). Greater improvement of working memory and sustained attention in response to methylphenidate treatment has also been demonstrated in children and adolescents with the G allele than in those without this allele (Polanczyk et al., 2007; da Silva et al., 2008; Cheon et al., 2009). However, even if several ADRA2A polymorphisms have repeatedly been associated with hyperactive and inattentive behaviour in psychiatric patients, considerably less is known of attention problems and overactivity in population based samples. The above listed evidence gives the reason to suggest the hypothesis that dysfunction of α_{2A} adrenoceptors may contribute to

Abbreviations: ADRA2A, Alpha 2A adrenergic receptor gene.

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similar behaviour among healthy individuals. With the exception of the study of Comings et al. (2000) which found the C-1291 G promoter polymorphism in ADRA2A associated with indirect hostility, irritability and verbal aggression in students and with impulsivity in normal adults, no study has addressed this question, and none has examined schoolchildren.

ADHD is a condition sensitive to environmental factors: several studies have shown that maltreated children exhibit significantly more severe symptoms of attention deficit and hyperactivity (Famularo et al., 1992; Ouyang et al., 2008). Moreover, the externalizing problems of the child may evoke certain parental responses, and it has also been demonstrated that hyperactive and inattentive children are often exposed to raised levels of negative parent–child relationships, family dysfunction and parenting stress (Johnston and Mash, 2001).

Environmental stressors are interacting with biological predisposition: aggressiveness, hyperactivity and inattention might have its origins in genes but are probably influenced by the way these genetic factors interact with and affect an individual's response to the environment. Some trends have been identified in the studies of gene–environment interaction in ADHD: there are gene–environment interactions, where adverse social factors increase the possibility of expression of risk gene alleles, and other gene–environment interactions where favourable social factors attenuate the genetic risks (Rutter et al., 2006; Sheese et al., 2007). It has recently been demonstrated that maternal criticism and warmth is moderating the effects of genes on ADHD severity (Sonuga-Barke et al., 2008). Adrenergic α_{2A} receptors mediate a number of physiological stress responses, including changes in cognition, cardiovascular function and metabolism (Lafontan and Berlan, 1993). The impact of ADRA2A genotype on behaviour may thus depend on early experience of stressful environmental factors like neglect or maltreatment in the family.

The purpose of this study was to clarify whether the ADRA2A genotype influences symptoms of ADHD in general population, and whether this would depend upon family relations. Thus the effect of the ADRA2A C-1291G polymorphism and warmth and maltreatment in family on inattentive, hyperactive and aggressive behaviour in a population representative sample of schoolchildren were examined.

2. Methods

2.1. The sample

The original sample of the European Youth Heart Study (1998/99) which was subsequently incorporated into the longitudinal Estonian Children Personality Behaviour and Health Study was used. The rationale for sample formation and procedure of data collection has been described in detail previously (Harro et al., 2001). In the present analysis, data of the younger cohort were used. Data were collected during the follow-up in 2004 when the subjects were 15.3 ± 0.5 years old. The present analysis included all adolescents who had been genotyped for ADRA2A polymorphisms and for whom teachers had completed SNAP-IV ($n = 429$, 196 boys, 233 girls). Parents and children gave their written informed consent before participating in the study, which was conducted according to the protocol approved by Ethics Review Committee on Human Research of the University of Tartu.

2.2. ADRA2A genotyping

The MspI polymorphism (rs1800544) in the promoter region of the ADRA2A gene was amplified by the polymerase chain reaction (PCR) using the primers and protocols previously reported (Lario et al., 1997; Mäestu et al., 2008). The forward primer was 5′-TCA CAC CGG AGG TTA-3′ and the reverse primer was 5′-TCC GAC GAC AGC GCG-3. If there was any doubt in determination the genotype correctly, the assay was run again. Genotypes were in Hardy–Weinberg equilibrium. ADRA2A genotype frequencies in boys and girls are presented in Table 1.

2.3. Psychological measures

Ratings on aggressiveness, motor restlessness, and concentration difficulties were obtained from the class teachers who had known the child for at least three years, using the 7-point Hyperactivity Scale of af Klinteberg (1988). The original study using this instrument in its Swedish version in a longitudinal design conservatively estimated the test–retest reliability for the rating variables at 0.80 (Magnusson et al., 1975; af Klinteberg, 1988). The teachers were instructed to use the boys and girls in their own class as reference groups. Hyperactivity score was calculated after af Klinteberg and Oreland (1995) by summing the scores of Motor Restlessness and Concentration Difficulties. Data of aggressiveness, motor restlessness and concentration difficulties were available for 402 adolescents. The teacher-report version of the SNAP-IV (Swanson et al., 2001) was also used to assess symptoms of ADHD among the adolescents. Each of the 18 items of the SNAP-IV provides a word-to-word description of a symptom of DSM-IV ADHD (American Psychiatric Association, 1994), and instructs the rater to indicate whether the child exhibits the symptom “not at all”, “just a little”, “pretty much”, or “very much”. The scores of SNAP-IV can be divided into Inattention and Hyperactivity/Impulsivity subscales. SNAP-IV scores were available for 429 adolescents.

Relationships in the family were measured by a child-report scale (Tartu Family Relationships Scale) (Paaver et al., 2008). It consists of four subscales (Closeness, Support, Abuse, and Misprize). The internal consistency reliability of those subscales is estimated to 0.94, 0.80, 0.83 and 0.86, respectively. Based on similarity in results in this as well as in a previous study (Paaver et al., 2008), in the presented analyses the subscales of Closeness and Support were added up under the name “Warmth in the family” and the subscales of Abuse and Misprize added up to “Maltreatment” in the presentation of data. Data about relations in the family were available for 379 adolescents.

2.4. Statistical analysis

The effect of ADRA2A genotype and family relations on the scores of Aggressiveness, Motor Restlessness, and Concentration Difficulties, and the sub-scores of SNAP-IV was analyzed by two and three-way analysis of variance (ANOVA). Groups with low and high warmth and maltreatment in the family were formed with the cut-off values at the median point. Scheffe post-hoc test was used to evaluate the differences between the groups, the level of significance was 5%. Spearman correlation was used to indicate the relationship between continuous variables.

3. Results

The mean ($\pm$SD) scores of the Hyperactivity scale of af Klinteberg (af Klinteberg, 1988), and SNAP-IV in boys and girls with CC, CG and GG genotypes are presented in Table 2. Boys had significantly higher scores on Aggressiveness, Motor Restlessness, Concentration Difficulties and Hyperactivity than girls: $F(1, 400) = 29.8$, 40.6, 27.1, and 40.1, respectively, $p < 0.0001$. Boys had also significantly higher scores of teacher-

Table 1
ADRA2A genotypes in the study participants.

ADRA2A genotype N (%)	CC	CG	GG	Total
Boys 196 (46%)	124 (63%)	64 (33%)	8 (4%)	196 (100%)
Girls 233 (54%)	132 (56%)	90 (39%)	11 (5%)	233 (100%)
Total 429 (100%)	256 (60%)	154 (36%)	19 (4%)	429 (100%)