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Short Communication

Resilience in refugee and Dutch adolescents: Genetic variability in the corticotropin releasing hormone receptor 1☆

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ABSTRACT

Relationships between the corticotropin-releasing hormone receptor 1 (CRHR1) [rs878886] and serotonin transporter promoter polymorphism (5-HTTLPR), with resilience and satisfaction with life were examined in 172 adolescents; 70 refugee adolescents living in the Netherlands and 102 non-refugee (Dutch) adolescents. Genetic variation in the CRHR1 was related with self-reported resilience and satisfaction with life, while the 5-HTTLPR polymorphism was not. These findings did not depend on being a refugee or a non-refugee (Dutch) adolescent and did hold after accounting for age, number of exposures to potentially traumatic events and gender. This implies that adolescents who are G-allele carriers of CRHR1 (rs878886) might be more susceptible to mental health problems following trauma, further suggesting innate differences in CRHR1 as a factor in resilience.

1. Introduction

Refugees are exposed to numerous stressors ranging from daily hassles to prolonged and recurrent traumatic experiences such as terror, persecution and violence. The ability to cope with these stressors varies greatly between individuals. Whereas many refugees suffer from serious mental health problems such as posttraumatic stress disorder and depression, others show resilience and are able to adapt successfully (Lustig et al., 2004). The phenomenon of resilience has garnered significant attention in recent years, but it is still puzzling as to why some individuals succumb to many hardships whereas others are able to successfully bounce back.

Various psychological, biological and sociocultural factors have been linked to resilience (Rutter, 2013). One such factor is the innate genetic makeup of individuals, i.e. genetic polymorphisms (Rutter, 2013). A particularly interesting polymorphism is located within the gene coding for the corticotropin-releasing hormone (CRH) receptor1 (CRHR1). CRH (also referred to as corticotropin releasing factor [CRF]) is a key neuropeptide in physiological and psychological responses to stress via regulation of activity in (amongst other regions) the hypothalamic–pituitary–adrenal (HPA)-axis (Hauger, Risbrough, Brauns, & Dautzenberg, 2006). In humans, this notion is supported by observed CRH dysregulation in mood and anxiety disorders, e.g. evident from alterations both in CRH levels (Sautter et al., 2003) and in CRH1 receptor expressions (Bissette, Klimek, Pan, Stockmeier, & Ordway, 2003).

The significance of CRH in stress and resilience can be traced back to research on rodents, which has yielded a convincing body of evidence (see Fox & Lowry, 2013, for an overview of animal findings). Despite the promising body of literature on animals, only a few studies have been performed in humans, most likely due to the lack of CRHR1 antagonists approved for human use. For this reason, the use of genetic proxies for CRF functioning is the current method of choice for research in humans. One promising proxy is a single nucleotide polymorphism (SNP) located within the 3′ UTR of CRHR1 (rs878886). In earlier studies, the minor G-allele of this SNP was linked to panic disorder (Keck et al., 2008) and to fear conditioned responding (Heitland, Groenink, Bijlsma, Oosting, & Baas, 2013; Heitland et al., 2016). A recent study on another SNP within CRHR1, namely rs17689918 that is in perfect linkage disequilibrium (LD) with rs878886, demonstrated that the minor allele of the SNP was associated with a phenotype characterised by heightened fear sensitisation and increased anxious apprehension (Weber et al., 2015). Moreover, the minor risk allele of rs17689918 was also shown

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to be associated with decreased CRHR1 mRNA expression in forebrains and amygdalae of human post-mortem brains, demonstrating the functional impact of these genetic polymorphisms (rs17689918 and rs878886) within CRHR1. Apart from these studies suggesting a link between CRHR1 and stress and psychopathology, CRHR1 has been associated with resilience directly (see Russo, Murrough, Han, Charney, & Nestler, 2012 for a discussion). As such, two human studies (Heim et al., 2009; Polanczyk et al., 2009) showed that genetic variability in CRHR1 confers protective effects against developing adult depression in subjects that experienced childhood trauma. Labermaier et al. (2014) provided a fitting animal model using mice that were exposed to adolescent chronic social stress. In their study, only the mice carrying certain CRHR1 gene variants showed a maladaptive neuroendocrine stress response in adulthood while their genetic counterparts were resilient.

Another polymorphism that is a prime candidate for an association with resilience is located within the promoter region of the serotonin transporter gene (5-HTTLPR) (Feder, Nestler, & Charney, 2009). Evidence suggests that this polymorphism is associated with greater reactivity of the HPA-axis to stress and that its long allele confers a biological resilience to mental health problems in the face of stress and adversity (Karg, Burmeister, Shedden, & Sen, 2011). In adolescents and young adults specifically, presence of the long allele has been associated with both resilience and life satisfaction (De Neve, 2011; Stein, Campbell-Sills, & Gelernter, 2009).

Drawing these strands together, the present study aimed to follow up on promising findings regarding the association between genetic variability in CRHR1 and 5-HTTLPR with regard to resilience and life satisfaction while at the same time applying these findings to both a specific target group of adolescent refugees with high trauma exposure and to non-refugee (Dutch) adolescents with various trauma exposure. Due to the occurrence of many changes during adolescence, it is a period during which the risk of developing psychopathology is heightened (Eiland & Romeo, 2013). Therefore, resilience is a particularly relevant concept when investigating adolescents. Nevertheless, only a limited number of studies have explored the relation between resilience and genetic variability in this age group. Furthermore, to the authors' knowledge, thus far, no studies have specifically examined the relationship between resilience and genetic differences in adolescent refugees. Given the rapidly growing number of refugees arising as a result of the proliferation of global conflicts, there is an increasing need to advance understanding of resilience in the face of adversity.

2. Methods

2.1. Participants and procedures

A cross-sectional study was conducted that comprised refugee and Dutch adolescents. Three hundred and seventy-nine adolescents from four high schools and seven asylum seeker centres (ASCs) throughout the Netherlands were invited to participate. Written permissions were obtained from one hundred and eighty-nine adolescents and their parent(s) for collection of buccal swabs. After DNA isolation, ten participants were excluded from the sample due to insufficient quality of isolated DNA and seven participants because of incomplete questionnaires. The final sample comprised 102 Dutch adolescents and 70 adolescent refugees. Subjects filled out the questionnaires in a quiet room setting and were at liberty at all times to ask for assistance from a trained psychologist and interpreter. All study procedures were approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

2.2. Measures

Sociodemographic data covering age, gender, country of origin and number of exposures to potentially traumatic events (PTEs) were collected. *Resilience*, defined as belief in one's personal competence and acceptance of self and life that enhances individual adaptation, was measured by the Dutch version of the Resilience Scale (RS) (Portzky, 2008). The RS consists of 25 items (mean score range = 1–4), with higher scores reflecting higher levels of individual resilience. *Satisfaction with life* was measured by the Dutch version of the Satisfaction with Life Scale (SWLS) (Arrindell, Meeuwesen, & Huyse, 1991). The SWLS consists of 5 items (mean score range = 1–7), with higher scores reflecting higher levels of life satisfaction. Both instruments have been the method of choice in many similar studies and are valid and reliable psychological questionnaires (RS: Ahern, Kiehl, Lou Sole, & Byers, 2006; SWLS: Pavot & Diener, 1993).

2.3. Genotyping

DNA was harvested by collecting buccal swabs that were frozen shortly after collection at −30 °C for later genotyping. All genotyping procedures were performed by BaseClear B.V., Leiden, The Netherlands. Genotyping protocols for both CRHR1 (rs878886) and 5-HTTLPR including rs25531 are validated and have been used before (for details, see Heitland et al., 2013, 2016).

For statistical analyses regarding CRHR1 (rs878886), we grouped C/G heterozygotes and G/G homozygotes as G-allele carriers (Heitland et al., 2013, 2016) and compared them to C/C homozygotes. Regarding the 5-HTTLPR, triallelic *5-HTTLPR*/rs25531 genotypes with low 5-HTT functioning (S/S, S/L_A, S/L_G, L_A/L_G and L_G/L_G) were pooled vs. a high 5-HTT functioning (L_A/L_A) group as commonly done (e.g., Gloster et al., 2015). Both CRHR1 and 5-HTTLPR/rs25531 were in Hardy-Weinberg equilibrium (*P*-values > 0.22).

3. Results

Genotype frequencies, sociodemographic and questionnaire data are shown in Table 1. Refugee participants appeared “slightly dissatisfied with life” and Dutch participants “slightly satisfied with life” (Pavot & Diener, 1993). Both groups scored “very high” on resilience (Portzky, 2008).

There was a significant association between CRHR1 rs878886 genotype and resilience ($F_{1,164} = 7.78$, $P = 0.006$, $\eta^2 = 0.05$) and quality of life ($F_{1,164} = 8.35$, $P = 0.004$, $\eta^2 = 0.05$), with G-allele carriers showing lower resilience and satisfaction with life scores compared with C/C homozygotes (Fig. 1). It is notable that this association was significant both with and without inclusion of covariates, such as age, number of PTEs and gender. There were no associations between 5-HTTLPR and resilience or quality of life, nor was there an interaction between CRHR1 rs878886 and 5-HTTLPR (*P*'s > 0.63). Furthermore, there was no interaction between any of the genetic variables and group (refugee or non-refugee group) (*P*'s > 0.09).

4. Discussion

Consistent with findings from earlier studies (Heitland et al., 2013, 2016; Keck et al., 2008; Weber et al., 2015), the presence of the CRHR1 risk allele (G) within rs878886 was linked to reduced resilience and quality of life; even after accounting for age, number of exposures to PTEs and gender. This finding fits well with the converging evidence from animal and human studies suggesting CRH as an important factor in resilience, stress related psychopathology and fear sensitivity.

The relations found in the present study were independent of descent, meaning that the demonstrated associations between CRHR1 genotype and quality of life and resilience did not depend on being a refugee or a non-refugee (Dutch) adolescent. This is consistent with the idea that allelic differences (nature) exert their effects ‘independently’ of nurture, but might have ‘additional’ effects depending on group compensatory mechanisms. However, it should be noted that