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Common variants of the mineralocorticoid and glucocorticoid receptor genes may contribute to pregnancy-related anxiety: a pilot study

Research Article

Natalia V. Chistiakova[1], Elena A. Sergienko[1], Kirill V. Savost'ianov[2]*

1 Department of Developmental Psychology, Institute of Psychology, Russian Academy of Science, Yaroslavskaya Ulitsa 13, 129366 Moscow, Russia

2 Department of Molecular Diagnostics, National Research Center GosNIIgenetika, 1st Dorozhny Proezd 1, 117545 Moscow, Russia

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Abstract: The hypothalamic-pituitary-adrenal (HPA) axis overactivity is thought to contribute to increased vulnerability to maternal stress. We hypothesize that functionally relevant polymorphic variants of the glucocorticoid (NR3C1) and mineralocorticoid (NR3C2) receptor genes mediating biological effects of cortisol, a major stress hormone, could also modulate the capacity to cope with pregnancy-related anxiety. Genomic DNA from the blood of 42 women with pregnancy-related anxiety and 42 age-matched women with normal pregnancy (5-6th months of gestation) were genotyped for markers rs6195 and rs10482605 of NR3C1 and two NR3C2 polymorphisms (rs5522 and rs2070951) using a Taqman allele discrimination assay. Serum total cortisol was measured using an ELISA technique. The allele Ser363 of rs6195 (the N363S polymorphism of NR3C1) was found to be associated with a higher risk of maternal stress (odds ratio (OR)=5.27; P=0.001). For NR3C2, the allele Val180 of rs5522 (I180V) also showed association with increased risk of neonatal stress (OR=1.97; P=0.038). Both predisposing gene variants were also associated with significantly elevated levels of cortisol in normally pregnant women and females with pregnancy-related anxiety. Our results suggest that pregnancy-related anxiety can be modulated by variants of NR3C1 and NR3C2 associated with increased basal cortisol levels. Thus, our findings provide evidence in support of the suggestion that elevated cortisol levels and HPA axis hyperactivity are implicated in pregnancy-related anxiety.

Keywords: *Pregnancy-related anxiety • HPA axis • Cortisol • Mineralocorticoid receptor • Glucocorticoid receptor • Polymorphism*

1. Introduction

The coping capacity for prenatal stress and pregnancy-related anxiety has been shown to be associated with preterm delivery in humans and animals [1]. The severity of the psychosocial stress has been found to negatively correlate with adverse pregnancy outcomes. Examples of psychosocial stressors may greatly vary including early life adversity events [2], irregular prenatal care, antenatal hospitalization, limited support from family and friends [3], poor housing conditions [4], low income, spouse's death [5], problematic neighborhood [6], work during pregnancy [7], and many others. The effect sizes of maternal stress on preterm birth in well-controlled prospective studies with relatively large sample sizes (>1000 subjects) have typically ranged between a 1.5-fold and twofold increase [8,9].

It has been hypothesized that that stress increases levels of cortisol and corticotrophin-releasing hormone (CRH), and increased CRH causes preterm birth [10].

* *E-mail: kir_savostianov@yahoo.com*

Under stress conditions, the hypothalamic-pituitary-adrenal (HPA) axis responds by releasing both cortisol and CRH. During pregnancy, cortisol stimulates the production of CRH in the placenta [11]. In several studies, higher levels of both cortisol and CRH have been found in medically complicated pregnancies [12-14]. A recent population study of 2.6 million pregnancies in USA revealed that stress in the late 2nd trimester (month 5 and 6) particularly increases risk of adverse pregnancy outcomes including shortened gestation age, preterm birth (odds ratio (OR)=1.24), low birth weight (OR=1.38), and small for gestational age (OR=1.25) [15].

Vulnerability windows of months 5 and 6 are likely to result from alterations in the HPA axis and associated stress-responsive molecular regulators. Mancuso et al. [16] reported that women with elevated CRH levels at 18 to 20 weeks gestation had significantly increased rates of preterm delivery compared to those who had normal CRH values. It seems that the late 2nd trimester of gestation plays a non-redundant role in the function of maternal and fetal HPA axis. By weeks 20-24 of pregnancy, both cortisol and adrenocorticotropic hormone levels in the maternal blood were shown to reach their maximal values that exceed initial levels by 2-5-fold [17,18]. This happens because the fetal HPA axis itself becomes fully functional by the 20th week of gestation, and further contribution of the maternal placenta as a source for fetal CRH becomes limited.

Thus, the HPA overactivity in response to stress is likely to be considered as a risk factor, which strongly predisposes to pregnancy distress and adverse pregnancy outcomes. The magnitude of the HPA response was shown to be deeply modulated by polymorphic variants of genes encoding the HPA axis components [19,20]. Indeed, we can hypothesize that HPA axis genetic polymorphisms may be also involved in controlling interpersonal variances in the coping capacity to prenatal stress.

Cortisol, a major glucocorticoid that is released in response to stress, and other glucocorticoid hormones produce behavioral changes, and one important target of glucocorticoids is the hypothalamus, which is a major controlling center of the HPA axis. Corticosteroids may play an important role in the relationship between stress, mood changes, and stress-related anxiety by interacting with hippocampal serotonin receptors 1A [21]. Expression of monoamine oxidase A, an important member of the serotonergic system involved in the degradation of serotonin, is differently regulated by both androgens and glucocorticoids *via* the HPA axis [22]. HPA axis hyperactivity associated with elevated cortisol levels may lead to the depletion of the serotonergic system through suppressing biosynthesis and release of serotonin in the brain [23]. Attenuated serotonergic function in the central nervous system is linked to various abnormal behaviors and psychiatric disorders including depression and anxiety-related illness [24]. Indeed, stress-induced HPA overactivity and impaired serotonergic function may be implicated in pregnancy-related anxiety.

Cortisol exerts its biological effects through binding to the mineralocorticoid and glucocorticoid receptors (encoded by the NR3C1 and NR3C2 gene respectively) [25]. Both receptors are located in the hippocampus, a region of the brain limbic system, in which cortisol could affect the production and release of various neurotransmitters and in turn influence human behavioral and personality traits [19]. Therefore, we can hypothesize that functionally relevant NR3C1 and NR3C2 polymorphisms, which alter the HPA axis activity and influence cortisol levels, can also be implicated in controlling capacity to cope with prenatal stress. In this study, we evaluated four functional variants of both genes for association with cortisol levels and pregnancy-related anxiety in two groups of pregnant women with normal and reduced resistance to maternal stress.

2. Materials and Methods

2.1. Subjects

The study population involved 84 pregnant women (the first pregnancy) selected from the patients of the Moscow Research Center of Obstetrics, Gynecology, and Perinatology who underwent medical genetic consulting during May, 2011 – March, 2012. The 'control' group included 42 women at 5-6 months of pregnancy (age 23.2±2.7 years, range 19-28.5 years) with normal pregnancy while the 'case' group consisted of 42 remaining subjects matched at age (22.5±2.8 years, range 17.5-27 years) and gestational duration (i.e., 5-6 months of pregnancy), who developed pregnancy-related anxiety.

The maternal prenatal anxiety was assessed using the Pregnancy-Specific Anxiety Scale [26]. The scale was tranlated by the authors (e.g. Chistiakova NV and Sergienko EA) and then tested in a total sample of over 1,200 pregnant women who visited the Moscow Research Center of Obstetrics, Gynecology, and Perinatology. The study protocol was approved by the Ethical Committee of the Center. The study was performed according to the bilateral agreement between the Center and the Institute of Psychology.

The scale was developed as an exploratory measure designed to assess women's level of anxiety about their pregnancy. Compared to the general measures of stress and emotion such as the Perceived Stress Scale

[27] and the Spielberger State Anxiety Scale [28], this scale is focused on the specific context within which stress occurs (such as a pregnancy, marriage, or other life event). This facilitates determining a key psychological component, which represents the most critical mechanism linking psychosocial factors with physiological outcomes.

Participants completed the scale by responding to the question "How have you felt about being pregnant in the past week including today?" They were asked to rate, on a 5-point scale (where 1 was "never" and 5 was "always"), how anxious, concerned, afraid, and panicky they felt about their pregnancy. These four items were chosen from a larger set of items created to assess pregnancy-specific affective states.

Maternal level of education and annual household income were assessed by interviews. Level of education was measured in years completed, with 11 years equivalent to completion of high school. The mean level of education was 12.8±2.3 years (*range* 7-16 years). The annual household income was measured using an ordinal scale ranging from 1 (under €2,000) to 13 (over €75,000), with categories designed to clearly differentiate lower income groups. The mean for the total sample was approximately €8,900.

Medical risk was calculated as the total number of medical risk factors present during each woman's pregnancy. The list of possible risk factors, developed in previous research, included 37 medical conditions [29]. Items in this list included factors such as a past history of infertility, urinary tract infections, anemia, vaginal infections, fever during pregnancy, and lifestyle factors such as smoking. Overall, the highest number of medical risk factors tallied for a given pregnancy was 5.00, with of mean of 1.75±1.25.

Eligible participants were approached by the research staff and asked to participate in the study. Informed consent was obtained and the rights of participants were protected in accordance with Human Subjects Research guidelines. Maternal blood samples were collected; so that neuroendocrine data could be obtained using serum bioassays

2.2. Biochemical measurements

Blood samples were collected at 8-9 AM, after an overnight fasting period of at least 10 h. Serum total cortisol was measured using an ELISA technique (Roche ES700, Roche Diagnostics Ltd, Lewes, UK), with a coefficient of variation of 3% at 498 nmol/L. Each sample was measured in triplicate.

2.3. DNA analysis

Total DNA was isolated from whole-blood samples pretreated with proteinase K using a standard protocol for extraction with phenol-chloroform (Fermentas, Vilnius, Lithuania).

All the polymorphisms studied were genotyped using a Taqman allele discrimination assay on a 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's manual. Polymorphic markers of the mineralocorticoid receptor (-2G>C [rs2070951] and I180V [rs5522]) were assessed as described by Klok et al. [30]. Two polymorphisms (NR3C1-1 [rs10482605] and N363S [rs6195]) located within the glucocorticoid receptor gene were analyzed as described by Geelhoed et al. [31]. Individual genotypes were determined using the SDS software (version 2.3, Applied Biosystems).

2.4. Statistical analysis

Data were analyzed with the SPSS/Win statistical package (version 16.0; SPSS Inc., Chicago, IL, USA). Results are given as mean ± S.D. or percentages. To compare quantitative data in groups of carriers of different genotypes, the unpaired Student's t-test was used. The test for Hardy–Weinberg equilibrium was performed using the χ^2 test. Genotype and allele frequencies in the 'case' and 'control' groups were compared using the Fisher's exact test. To assess the extent to which the various genotypes were associated with a pregnancy-related anxiety, ORs and 95% confidence intervals (CI) were estimated using the Calculator for Confidence Intervals of Odds Ratio [32]. Standardized linkage disequilibrium (LD) values (*D*' and r^2 values) were measured using the 2LD software [33]. In the quantitative analysis of serum levels of cortisol, statistical significance of differences between the groups was tested using non-parametric tests: Kruskal-Wallis rank sum test for comparison of three genotypes and Mann-Whitney U-test for comparisons between two groups. *P*-values of less then 0.05 were considered significant.

3. Results

Main characteristics of participants of two studied groups are shown in Table 1. Compared to the cases, control subjects had significantly higher education level ($P<0.01$) and annual household income ($P<0.0001$),

while serum cortisol level was significantly reduced (P<0.001).

For all the polymorphisms studied, observed genotype frequencies obeyed the Hardy-Weinberg equilibrium (data not shown). In the 'case' group, the variant V180 of NR3C2 was significantly overrepresented compared to the controls (P=0.038) (Table 2). Similarly, the variant S363 of NR3C1 was significantly

Table 1. Key characteristics of two groups of pregnant women with normal and altered resistance to maternal stress

Variable	Cases (n=42)	Controls (n=42)	P-value*
Age, years	23.2±2.7	22.5±2.8	0.78
Duration of gestation, months	5.9±0.4	6.3±0.4	0.63
Medical risk	2.15±1.45	1.5±1.1	0.16
Annual household income, €	5,480±1,620	12,300±2,950	<0.0001
Level of education, years	10.3±2.1	13.9±2.4	<0.01
Cortisol level, nmol/L	677±160	469±107	<0.001

Values are mean ± S.D. or percentages.
**Student's t-test*

Table 2. Association of NR3C1 and NR3C2 polymorphisms with pregnancy-related anxiety

Allele/ genotype	Frequency, n (%) Cases (n=42)	Controls (n=42)	OR (95% CI)	P-value (Fisher's test)
MR(-2)G>C (rs2070951)				
G/G	7 (16.7)	11 (26.2)	Reference	
G/C	18 (43.3)	21 (50.0)	0.74	0.77
C/C	17 (40.0)	10 (23.8)	2.67	0.14
Allele G	32 (38.1)	43 (51.2)	Reference	
Allele C	52 (61.9)	41 (48.8)	1.7	0.12
MR I180V (rs5522)				
I/I (A/A)	12 (28.6)	20 (47.6)	Reference	
I/V (A/G)	23 (54.7)	20 (47.6)	1.91	0.24
V/V (G/G)	7 (16.7)	2 (4.8)	5.83	0.057
Allele I (A)	47 (56.0)	60 (67.9)	Reference	
Allele V (G)	37 (44.0)	24 (32.1)	1.97 (1.04-3.73)	0.038
GR NR3C1-1 (rs10482605)				
T/T	19 (22.6)	23 (54.3)	Reference	
T/C	20 (45.3)	18 (43.3)	1.35	0.66
C/C	3 (7.1)	1 (2.4)	3.63	0.34
Allele T	58 (69.0)	64 (77.2)	Reference	
Allele C	26 (31.0)	20 (23.8)	1.43 (1.04-1.42)	0.39
GR N363S (rs6195)				
N/N (A/A)	25 (59.5)	38 (90.5)	Reference	
N/S (A/G)	13 (31.0)	3 (7.1)	6.59	0.65
S/S (G/G)	4 (9.5)	1 (2.4)	5.58 (1.7-25.5)	0.0043
Allele N (A)	63 (75.0)	79 (94.0)	Reference	
Allele S (G)	21 (25.0)	5 (6.0)	5.27 (1.88-14.75)	0.001

GR, glucocorticoid receptor; MR, mineralocorticoid receptor; OR, odds ratio

Table 3. Serum cortisol levels in carriers of different genotypes of rs6195 (NR3C1) and rs5522 (NR3C2)

Patients	NR3C1 genotypes (rs6195)	Serum cortisol level, nmol/L	P-value (Kruskal-Wallis test)	Patients	NR3C2 genotypes (rs5522)	Serum cortisol level, nmol/L	P-value (Kruskal-Wallis test)
Cases	N/N (n=25)	659±179	0.0007	Cases	I/I (n=12)	663±163	0.0011
	N/S (n=13)	693±135*			I/V (n=23)	698±151****	
	S/S (n=4)	718±144**			V/V (n=7)	713±168*****	
Controls	N/N (n=38)	460±102	0.017	Controls	I/I (n=20)	460±122	0.0086
	N/S (n=3)	514±127***			I/V (n=20)	493±95******	
	S/S (n=1)	496			V/V (n=2)	505±104	

Values are mean ± S.D. or percentages.
** N/S vs. N/N: P = 0.0072 (cases; Mann-Whitney U-test)*
*** S/S vs. N/N: P = 0.0033 (cases; Mann-Whitney U-test)*
**** N/S vs. N/N: P = 0.028 (controls; Mann-Whitney U-test)*
***** I/V vs. I/I: P = 0.0061 (cases; Mann-Whitney U-test)*
******V/V vs. I/I: P = 0.0045 (cases; Mann-Whitney U-test)*
******* I/V vs. I/I: P = 0.0017 (controls; Mann-Whitney U-test)*

more frequent in the group of women with pregnancy-related anxiety compared to the women with normal pregnancy (P=0.001). Indeed, the presence of the allele V180 of the mineralocorticoid receptor and allele S363 of the glucocorticoid receptor was associated with increased risk of maternal stress (OR=1.97 and 5.27, respectively). No significant differences between the 'case' and 'control' groups were found for markers rs10482605 of NR3C1 and rs2070951 of NR3C2.

According to the HAPMAP data, markers rs6195 and rs10482605 of NR3C1 lie within the same LD block [34] and are in moderate but significant pair-wise LD (D'=0.63, r^2=0.55, P<0.001). Similarly, both NR3C2 polymorphisms, rs5522 and rs2070951, are also located in the same LD block [19] and have weak but still significant LD to each other (D'=0.59, r^2=0.52, P<0.01). Since the intermarker pair-wise LD is moderate, the haplotype analysis is unlikely to add much to the association results. Indeed, we did not analyze the haplotypes for possible association with pregnancy-related anxiety.

In order to explain pathophysiological significance of observed associations, we studied whether risk markers rs5522 and rs6195 are associated with serum cortisol levels (Table 3). In both groups, the susceptibility gene variants (NR3C1 S633 and NR3C2 V180) were related to elevated serum levels of cortisol. Therefore, the predisposing role of these genetic risk markers may result from their association with impaired HPA axis function (i.e. HPA overactivity) in response to psychosocial stress that in turn could contribute to inducing pregnancy-related anxiety.

4. Discussion

We found that polymorphic variants of the mineralocorticoid and glucocorticoid receptors associated with elevated serum cortisol levels contribute to increased risk of pregnancy-related anxiety.

Polymorphic variants of the mineralocorticoid and glucocorticoid receptors were shown to be able to directly influence the HPA axis activity and cortisol levels [19]. The NR3C1 and NR3C2 gene polymorphisms assessed in this study were chosen due to the proven effects of these markers to the HPA axis functionality.

In NR3C2, the marker rs2070951 is located in two nucleotides upstream the start ATG codon (at position -2). The major allele G is associated with 2-fold reduction of receptor activation by cortisol and dexamethasone and with elevated basal levels of cortisol [35, 36]. The minor allele C of this marker was shown to form with the major allele of Ile160 of marker rs5522 a haplotype -2C/I180 associated with the highest expression and transactivation activity of the mineralocorticoid receptor and indeed with higher cortisol levels and HPA activity in response to psychosocial stress (Trier Social Stress Test, TSST) [37].

Marker rs5522 (I180V) itself causes an amino acid substitution of isoleucine to valine, and the Val180 variant of the receptor requires significantly higher doses of cortisol to be activated *in vitro*. The allele V180 of NR3C2 was associated with increased basal cortisol levels and augmented HPA-dependent response to a psychosocial stressor (TSST) [38]. These findings are in agreement with our data on increased levels of cortisol in pregnant women who were homozygous for the risk genotype V/V. Furthermore, Bogdan et al. [39] reported that psychiatrically healthy carriers of the Val180 allele had reduced ability to modulate behavior as a function of reward when facing an acute, uncontrollable stressor. This observation is in line with our finding on the association of the Val180 variant of the mineralocorticoid receptor with decreased capacity of pregnant women who carry this allele to cope with prenatal stress.

The polymorphic marker NR3C1-1 (rs10482605) located in the promoter region of the glucocorticoid receptor gene was found to modulate expression of NR3C1. The minor allele C of rs1048260 showed reduced transcriptional activity under unstimulated conditions and under stimulation by cortisol and dexamethasone in two brain-derived cell lines [40]. The amino acid substitution of asparagine to serine at codon 363 (N363S, rs6195) lies outside of the steroid-binding domain of the receptor molecule [41]. The Asp363 and Ser363 receptor variants showed similar capacity to activate target genes in *in vitro* assays [41,42]. However, in a mitogen-induced cell proliferation assay, lymphocytes derived from homozygous S/S carriers had a trend towards greater sensitivity to dexamethasone compared to the cells from homozygotes N/N [42]. These observations were further confirmed by Russcher et al. [43] suggesting for relation of the N363S variant of NR3C1 to elevated sensitivity to glucocorticoids and increased transactivating capacity. The correlation between the presence of the Ser363 allele and enhanced cortisol response to psychosocial stress was shown in several studies [44-46] thereby supporting our findings on increased cortisol levels observed in pregnant women homozygous for S/S and a predisposing role of this polymorphism to maternal stress.

Unfortunately, our present knowledge on the role of genetic background in prenatal maternal stress is scarce. In this field, studies were mainly focused on the assessment of genetic susceptibility to preterm birth, and the most consistent data were obtained for variants of the maternal tumor necrosis factor-alpha, a proinflammatory cytokine, associated with spontaneous preterm delivery caused by infection and chronic stress [47]. There is some evidence on a relation between the variants of the renin-angiotensin system components and psychological characteristics of pregnant women in a small sample of 56 Russian females [48,49]. However, these results need to be independently replicated in other population samples.

The role of the NR3C1 and NR3C2 genes in pregnancy-related anxiety found in our study is not surprising since both receptors are directly involved in mediating the effects of the HPA axis on behavioral and mood changes in the central nervous system. The variants of both receptors were shown to contribute to depression, which also belongs to stress-related disorders [50], and may share common pathophysiological mechanisms with anxiety. However, due to the small size of the population tested in our study, we cannot form strong conclusions about the impact of the HPA axis genes on prenatal stress. This report is a pilot study, and further investigations involving enlarged population samples are necessary to clarify the contribution of the NR3C1 and NR3C2 genes to maternal stress.

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