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Severity of eating disorder symptoms related to oxytocin receptor polymorphisms in anorexia nervosa

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ABSTRACT

Oxytocin is a peptide hormone important for social behavior and differences in psychological traits have been associated with variants of the oxytocin receptor gene in healthy people. We examined whether single nucleotide polymorphisms (SNPs) of the oxytocin receptor gene (OXTR) correlated with clinical symptoms in women with anorexia nervosa, bulimia nervosa, and healthy comparison (HC) women. Subjects completed clinical assessments and provided DNA for analysis. Subjects were divided into four groups: HC, subjects currently with anorexia nervosa (AN-C), subjects with a history of anorexia nervosa but in long-term weight recovery (AN-WR), and subjects with bulimia nervosa (BN). Five SNPs of the oxytocin receptor were examined. Minor allele carriers showed greater severity in most of the psychiatric symptoms. Importantly, the combination of having had anorexia and carrying either of the A alleles for two SNPS in the OXTR gene (rs53576, rs2254298) was associated with increased severity specifically for ED symptoms including cognitions and behaviors associated both with eating and appearance. A review of psychosocial data related to the OXTR polymorphisms examined is included in the discussion. OXTR polymorphisms may be a useful intermediate endophenotype to consider in the treatment of patients with anorexia nervosa.

1. Introduction

Eating disorders (ED) are complex psychiatric illnesses with environmental, cognitive, and biological contributions to their etiology and manifestation (Becker, 2004; Bulik et al., 2007; Herpertz-Dahlmann et al., 2011; Kaye et al., 2011). Biological pathway differences that contribute to a mental illness, but are not necessarily describing all aspects of the illness, have been called intermediate phenotypes (Flint et al., 2014). Improving our understanding of intermediate phenotypes within EDs may allow for individualized treatments targeted to the specific mechanistic dysfunctions.

Social cognitive differences have been proposed as a specific intermediate phenotype related to anorexia nervosa (Harrison et al., 2012; Zucker et al., 2007). Reduced social cognitive function has been observed using psychological assessments in both acutely ill and weight-recovered subjects with anorexia nervosa (Oldershaw et al., 2011; Tchanturia et al., 2011). Additionally, neural differences in the engagement of social cognitive regions during social tasks have been observed (McAdams and Krawczyk, 2011; Schulte-Ruther et al., 2012).

Oxytocin is a neurotransmitter important for many forms of both social behavior including pair-bonding, maternal attachment, and group identification, as well as appetite suppression (Leng et al., 2008a; Leng et al., 2008b). Oxytocin has been linked to many psychiatric illnesses, including autism, EDs, addiction, schizophrenia, and post-traumatic stress disorder (Maguire et al., 2013; Marazziti and Catena Dell'osso, 2008). Most recently, Kim et al. (2014b) reported increased methylation of CpG dinucleotides in the oxytocin receptor (OXTR) gene in a small sample of patients with anorexia nervosa, a modification that has previously been associated with reduced expression of oxytocin receptors in the brain (Gregory et al., 2009).

Polymorphic and epigenetic changes in the OXTR gene have been related to psychological and neural differences in healthy individuals. One OXTR single nucleotide polymorphism (SNP), the A allele of rs2254298, has been associated with the volume of the amygdala, a structure associated with anxiety and fear (Inoue et al., 2010). This polymorphism has also been associated with a sexual dimorphism related to the expressed psychological phenotype, with male carriers expressing autistic traits and female carriers expressing anxiety traits (Chen and Johnson, 2012). Another OXTR SNP, the A allele of rs53576, has been associated with low levels of self-esteem, optimism, and mastery (Saphire-Bernstein et al., 2011). This SNP also prevents social support from

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reducing the cortisol response of healthy individuals in a laboratory stress-induction procedure (Chen et al., 2011a). We hypothesized that the minor alleles of OXTR would be more common in patients with EDs, because high anxiety, low-self esteem, and difficulty managing social stresses are also common amongst these patients (Grilo et al., 2012; Gual et al., 2002; Herpertz-Dahlmann et al., 2001).

2. Methods

2.1. Participants

A total of 124 female participants over age 18 were included in this study. The study was approved by the institutional review board of the University of Texas at Southwestern Medical Center, and participants were recruited from the public and ED treatment programs in the Dallas-Fort Worth area.

Subjects came to an initial appointment at which they provided written informed consent to participate in this study. All subjects were then interviewed using the Structured Clinical Interview for DSM-IV disorders (SCID-RV, (First et al., 2002)). A detailed history of all past and current ED symptoms was also obtained. Subjects were classified into four groups. Healthy comparison subjects (HC, $n=35$) were those subjects without any ED symptoms that did not have any first-degree relatives with an ED. Subjects currently with anorexia (AN-C, $n=36$), were all subjects who had met full DSM-IV criteria for anorexia nervosa during the preceding 12 months. Subjects currently in weight-recovery from anorexia (AN-WR, $n=26$), were all subjects who had met DSM-IV criteria for anorexia nervosa in their lifetime but had maintained a BMI greater than or equal to 19.0 for 24 months or longer. Subjects in the BN group were all subjects that had met DSM-IV criteria for bulimia nervosa in their lifetime and had never met DSM-IV criteria for anorexia nervosa (BN, $n=27$).

2.2. Measures

The Wechsler Abbreviated Scale of Intelligence (WASI, (Pearson Corporation, 1999)) was administered to provide an estimate of intelligence quotient. Three clinician-based measures were used to assess current depression, anxiety, and ED symptoms. The Quick Inventory of Depressive Symptomalogy (QIDS-CR, (Rush et al., 2003)) is a 16 question clinician-administered inventory of depressive symptoms. The Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A, (Shear et al., 2001)) is a clinician-administered assessment assessing anxiety symptoms in fourteen categories. The Yale Brown Cornell Eating Disorder Survey (YBC-EDS, (Mazure et al., 1994; Sunday et al., 1995)) is a self-report check list followed by a 22-statement clinician-administered ED inventory for current eating preoccupations and rituals.

Each participant also completed a self-report packet. The Young-Brown Obsessive-Compulsive Symptoms (Y-BOCS, (Woody et al., 1995)) provided an overall estimate of obsessions and compulsions, including those unrelated to the ED. The 26-item Eating Attitudes Test (EAT-26, (Berland et al., 1986)) provided a second measure of ED behaviors with subscales for dieting behavior (EAT-D), bulimia behaviors (EAT-B), and oral control behaviors (EAT-O). The 34-item Body Shape Questionnaire (BSQ, (Rosen et al., 1996)) provided a measure of ED symptomatology related to shape and weight concerns.

2.3. DNA processing

Blood samples were collected from patients and submitted to McDermott Center for Human Growth & Development Human Genetics Clinical Laboratory located at UT Southwestern Medical Center in Dallas, TX, for processing and isolation of DNA. Samples were quantified using nanodrop and diluted in 96 well plates. The plated samples were then sent for Single Nucleotide Polymorphism (SNP) analysis at McDermott Center for Human Growth & Development DNA Sanger Sequencing Core located at UT Southwestern Medical Center in Dallas, TX. All oxytocin receptor SNPs were premade and purchased from Applied Biosystems by life technology: rs53576/CG (G/A), rs2254298 (G/A), rs2228485/CG_15917821_20 (T/C), rs2268493/CG_3290331_1 (T/C), rs918316/CG_7622139_10 (T/C).

2.4. Statistical analysis

All data was collected using standard data forms and entered into a Microsoft Excel spreadsheet for analysis using The Statistical Package for the Social Sciences (SPSS) software (version 21). Genotypic/haplotype differences within each patient group (HC, AN-C, AN-WR, and BN) were examined using independent Student's *T*-tests. Analysis of Variances (ANOVA) were calculated to examine associations between genotype/haplotype and subject groups (HC, AN-C, and AN-WR). A p value of <0.05 was considered significant.

3. Results

3.1. Demographic and clinical profile of study groups

The groups consisted of females between the ages 18–67 years old and grouped based on clinical diagnosis at the time of enrollment (HC, AN-C, AN-WR, BN). The subject population was primarily Caucasian (77–100%) with less than eight individuals per group of other races and ethnicities (Asian, African Americans, or Native Americans) and primarily Non-Hispanic (92–100%). One-way ANOVA's indicated that the subjects recruited did not differ across groups in age at enrollment, years of education or intelligence measured by the Wechsler's Assessment Scale for Intelligence (WASI). A one-way ANOVA ($F=18.69$, $p<0.001$) followed by Tukey's post-hoc analysis indicated that the current body mass index (BMI) was similar in HC (22.9±0.8), AN-WR (22.9±0.7) and BN (23.4±0.7) groups with only the AN-C group (17.9±0.3) differing from all other groups ($p<0.05$). One-way ANOVA ($F=6.39$, $p<0.003$) followed by Tukey's post-hoc analysis within the clinical population suggest age of onset of the ED was lower in the AN-WR (13.5±0.7) group compared to either the AN-C (16.7±0.7) and BN (17.8±1.2) groups.

3.2. OXTR SNP frequency not predictive of development of ED

Table 1 is the genotype frequency of all the OXTR SNPs (rs53576, rs2254298, rs2228485, rs2268493 and rs918316) analyzed. Table 2 shows the minor allele frequency for all the SNPs and Chi-square (χ^2) analysis for all the clinical groups compared HC. The results indicated that none of the OXTR SNPs were predictive of development of anorexia nervosa or bulimia nervosa. Haplotype combinations were also examined for any combination that had at least five subjects per haplotype group with no significant findings (data not shown).

3.3. OXTR SNP associated with ED clinical assessments

In order to examine if any of the OXTR SNPs or haplotype combinations of SNPs had an effect on any of the ED symptoms or psychological measures, two-way ANOVA's between group (HC, AN-C, AN-WR, BN) and SNP or haplotype were conducted for all individual SNPs or haplotype combinations. Two-way ANOVAs between group and rs53576 (GG vs. C carriers) indicated

Table 1
Genotype frequency of OXTR SNPs.

Genotype	HC	AN-C	AN-WR	BN
rs53576				
GG	48.6% (17)	58.3% (21)	38.5% (10)	55.6% (15)
GA	45.7% (16)	27.8% (10)	50.0% (13)	37.9% (11)
AA	5.7% (2)	13.9% (5)	11.5% (3)	3.7% (1)
rs2254298				
GG	80.0% (28)	63.9% (23)	76.9% (20)	81.5% (22)
GA	20.0% (7)	36.1% (13)	19.2% (5)	18.5% (5)
AA			3.8% (1)	
rs2228485				
TT	54.3% (19)	44.4% (16)	42.3% (11)	51.9% (14)
TC	28.6% (10)	41.7% (15)	42.3% (11)	48.1% (13)
CC	17.1% (6)	13.9% (5)	15.4% (4)	
rs2268493				
TT	57.1% (20)	50.0% (18)	46.2% (12)	44.4% (12)
TC	37.1% (13)	41.7% (15)	46.2% (12)	44.4% (12)
CC	5.7% (2)	8.3% (3)	7.7% (2)	11.1% (3)
rs918316				
TT	85.7% (30)	77.8% (28)	88.5% (23)	77.8% (21)
TC	14.3% (5)	19.4% (7)	11.5% (3)	22.2% (6)
CC		2.8% (1)		

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