Rare missense coding variants in oxytocin receptor (OXTR) in schizophrenia cases are associated with early trauma exposure, cognition and emotional processing

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ABSTRACT

Background: Oxytocin is a peptide hormone that influences the integration of social cognition with behavior and affect regulation. Oxytocin also prominently directs the transition of neuronal GABA neurotransmission from excitatory to inhibitory after birth. The oxytocin receptor (OXTR) is linked to schizophrenia, a heterogeneous syndrome. Relationships of OXTR polymorphisms with specific clinical features could aid in evaluating any role of oxytocin in the pathogenesis of schizophrenia.

Method: Schizophrenia cases with rare missense coding OXTR single nucleotide variants (SNVs) were identified from a well-characterized sample of cases and controls who were assessed for symptoms, cognition and early life trauma.

Results: Five of 48 cases showed rare OXTR variants. Compared to the other cases they had less severe negative symptoms (deficits in emotional expression and motivation) and less severe general psychopathology scores (depression and anxiety). They demonstrated lower nonverbal (performance) than verbal intelligence due to deficient perceptual organization and slow processing speed. They also reported greater early trauma exposure (physical and sexual abuse and emotional trauma).

Conclusion: Cases carrying rare OXTR SNVs had less negative and affective symptoms than other cases, but similar psychotic symptoms, along with specific cognitive deficits. The clinical characterization of these cases occurred in association with environmental exposure to early trauma, especially sexual abuse, which may have influenced the expression of schizophrenia in subjects harboring specific SNVs in the OXTR.

1. Introduction

Oxytocin has important roles in animal and human social behavior, ranging from maternal attachment to fear extinction (Meyer-Lindenberg et al., 2011). In schizophrenia, a condition that includes core social deficits, there are conflicting findings about oxytocin and symptom severity (Cochran et al., 2013). Early studies of cerebrospinal fluid (CSF) found higher levels of oxytocin in individuals with schizophrenia than controls, especially in those with paranoid schizophrenia (Beckmann et al., 1985). Recent studies that consider domains of psychopathology, demonstrate a relationship between higher plasma oxytocin levels with less negative symptoms (Sasayama et al., 2012). One study found that higher oxytocin levels significantly predicted less severe positive symptoms and overall psychopathology in female cases.
while higher levels were associated with more prosocial behavior in male and female cases behavior (Rubin et al., 2010).

The interpretation of CSF and circulating oxytocin levels depends on the presence of a functionally intact oxytocin receptor (OXTR). Schizophrenia risk is linked to single nucleotide variants (SNVs) in the OXTR gene among others, thus mean CSF oxytocin levels may not adequately define the effect of OXTR in modulation of the disorder. These genetic association studies correlated OXTR SNVs in a case-control design (Souza et al., 2010; Montag et al., 2013) with severity of negative symptoms and good clinical response to clozapine (Souza et al., 2010).

OXTR is expressed in the amygdala and other basal nuclei such as nucleus of Meynert and hypothalamic nuclei, as well as Broca’s area and in the anterior cingulate cortex (Loup et al., 1991; Boccia et al., 2013). Through these receptors, oxytocin exerts significant modulatory effects on the brain regions related to social cognition, and social behavior with affect regulation. Together, the relationships between OXTR and psychotic symptoms, social skills, affect expression and cognition in the literature suggests there may be an oxytocin-related phenotype of schizophrenia. In addition to the severity of positive and negative symptoms, there are other clinical characteristics of schizophrenia that have been related to OXTR. In a follow up study relating OXTR SNVs to schizophrenia risk (Montag et al., 2012), a significant interaction was demonstrated between an intronic SNV of OXTR and ‘empathic concern’ in schizophrenia (Montag et al., 2012).

It is feasible that early environmental effects, including parental bonding and trauma, could act through alterations in oxytocin expression, producing an epiphenotype as a consequence of gene-environment interactions (Unternaehrer et al., 2015). This is suggested by the results of a study on parental bonding, showing greater DNA methylation in oxytocin target sequences in association with low maternal care. Similarly, prenatal maternal stress is associated with higher OXTR methylation levels in neonates (Ceci et al., 2014). Convergent studies report relationships among DNA methylation at different sites in the OXTR gene and lesser oxytocin modulation in the brain (Ksuits et al., 2001; Dadds et al., 2014). Higher oxytocin plasma levels predict the correct identification of facial emotions (Goldman et al., 2008), enhanced social cognition (Averbeck et al., 2011) and trustworthiness perceptions (Zak et al., 2005).

In schizophrenia cases, a significant negative association between OXTR gene methylation and cognitive performance is reported which was independent of demographic variables and antipsychotic medication (Grove et al., 2016). Methylation was associated with more impaired emotion recognition and with reduced temporal-limbic and prefrontal volumes in female cases (Rubin et al., 2016). Alterations in the DNA methylation of the OXTR gene might underlie some of the differences in stress-reactivity shown between schizophrenia cases and controls (Engert et al., 2010), and contribute to the increased risks for later mental disorders following low parental care (Enns et al., 2002). These relationships await testing with respect to schizophrenia.

Evidence of a relationship between neurodevelopment and oxytocin activity is emerging. Oxytocin levels and OXTR play an important role in the switch from excitatory to inhibitory function of the GABA neurotransmission, which occurs immediately before birth and throughout brain maturation (Tyzio et al., 2006; Valeeva et al., 2013). Intracerebroventricular oxytocin administration in rats significantly increased gene expression for neurotrophic factors, protein levels for hippocampal microtubule-associated protein 2 (MAP2), and synapsin 1. The behavioral consequences included impaired object recognition, consistent with a role for oxytocin in regulating neuroplasticity through neuronal growth factors to influence cytoskeletal proteins and behavior (Havranek et al., 2015). Disruptions in oxytocin signaling may contribute to psychiatric vulnerability through neurotrophin-mediated pathways for neurodevelopment and neuroplasticity, particularly in conjunction with environmental stressors.

The role of early life experiences with respect to OXTR genetic variability in schizophrenia is of particular interest, as the disorder has strong neurodevelopmental antecedents, is associated with early adversity and is frequently marked by early social dysfunction. Whether or not the oxytocin receptor system is a major component or modulator of schizophrenia or a particular illness phenotype, remain to be elucidated.

Schizophrenia is a heterogeneous syndrome, so the current approach focused on a portion of cases in a well-characterized sample harboring rare missense coding SNVs in the OXTR gene, even though other genes may be involved in the modulation of this pathway. In the current analysis, cases with and without such SNVs were compared with respect to demographics, psychopathology, cognitive measures and exposure to early adversity.

2. Material and methods

2.1. Ascertainment and characterization of cases

Cases with schizophrenia or schizoaffective disorder, ages 18–55 years, were recruited from treatment settings at Bellevue Hospital Center and the New York University Medical Center. Human subjects approvals were obtained from the IRB at both institutions and all subjects signed written informed consent for the study. Diagnoses were determined by best estimate diagnostic procedures that included the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) conducted by reliable master’s level diagnosticians. The inter-rater reliability was $\kappa = 0.95$ for DSM-IV diagnosis and $\kappa = 0.80$ for individual symptoms. Symptoms were assessed with the Positive and Negative Syndrome-Scale (PANSS) which separately generates positive, negative and general psychopathology measures (Kay et al., 1987). Mood and anxiety symptoms were assessed by Hamilton Depression (Hamilton, 1960) and Anxiety (Hamilton, 1959) rating scales and the Young Mania Rating Scale (Young et al., 1976). The Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) assessed Verbal IQ, Performance IQ, Full Scale IQ, and the subtest indices for Verbal Comprehension, Perceptual Organization, Working Memory, and Processing Speed. Early trauma exposure was assessed using the Early Trauma Inventory (ETI) (Bremner et al., 2000), a clinically administered comprehensive assessment of physical, emotional and sexual abuse, as well as general trauma experienced before and after the age of 18 years, including age of occurrence, frequency, identity of the perpetrators and the impact of the event.

2.2. Sample size and DNA source

Targeted exome capture of 48 non-related schizophrenia-affected individuals of diverse ethnicity was conducted on DNA derived from peripheral leukocytes.

2.3. Targeted exome capture and variant calling

Cases underwent targeted exome capture as described in detail in previous studies (Kranz et al., 2015). Genomic DNA was isolated from leukocytes derived from whole blood using a simple salting out procedure. The DNA (500 ng) was sheared to an average of 150 bp. Barcoded libraries were prepared using the Kapa Low-Throughput Library Preparation Kit Standard Libraries and amplified using the KAPA HiFi Library Amplification Kit (Kapa Biosystems) (8 cycles). Quantification was performed using Qubit Fluorometric Quantitation (Invitrogen) and Agilent Bioanalyzer. An equimolar pool of the 4 barcoded libraries (300 ng each) was used as input to exon capture using one reaction tube of the custom Nimblegen SeqCap EZ (Roche) with custom probes targeting the coding exons of the genes of interest. Capture by hybridization was performed according to the manufacturer’s protocols with the following modifications: 1 nmol of a pool of blocker oligonucleotides and post-capture PCR amplification using the KAPA HiFi
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