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Research paper

Attempted suicide and oxytocin-related gene polymorphisms

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ABSTRACT

Background: Oxytocin may moderate prosocial behaviors, but has also been implicated in negative mental health outcomes. A single-nucleotide polymorphism (SNP) of the oxytocin receptor gene (*OXTR*), rs53576, and a SNP of the *CD38* gene, which regulates oxytocin secretion, rs3796863, have been associated with depression and suicidal ideation.

Methods: We conducted an exploratory study investigating the relationship of these two SNPs to history of suicide *attempt*. Secondary analyses explored relationships of genotype with sex, diagnosis, history of abuse, depression, suicidal ideation, and attachment and personality traits. Subjects were depressed adults with DSM-IV major depressive disorder (MDD; $n = 161$) or bipolar disorder (BD; $n = 75$).

Results: The A allele of rs53576 was associated with suicide attempt history. A differential effect of rs3796863 genotype on suicide attempt risk was found by diagnosis. In the BD sample, CC and AC genotypes were associated with higher odds of suicide attempt compared to AA, while in the MDD sample, AC subjects were more likely than CC subjects to have made an attempt.

Limitations: Our assessment of social sensitivity was limited to measures of attachment style and abuse history and did not differentiate between types of abuse. Plasma oxytocin was not measured.

Conclusions: These findings add to evidence for the involvement of oxytocin in suicide attempts and identify a potential biomarker for differentiating depressed attempters from non-attempters.

1. Introduction

About 800,000 people die by suicide every year, and many more make nonfatal attempts (World Health Organization, 2017). A 28% increase in the U.S. suicide rate from 1999 to 2016 (https://webappa.cdc.gov/sasweb/ncipc/mortrate.html; CDC, 2017) indicates the urgent need for more effective suicide prevention. Adoption and twin studies support the presence of a substantial genetic component in the predisposition to suicide and nonfatal suicide attempts, which is independent of the heritable component of the associated psychiatric disorder (Brent and Mann, 2005; Fu et al., 2002; Statham et al., 1998; Voracek and Loibl, 2007). However, limited progress has been made in identifying specific genes related to suicide and suicide attempts. Investigating genetic associations and gene-environment interactions may help identify biomarkers that could improve the targeting and thereby effectiveness of prevention efforts.

Oxytocin, a neuropeptide that plays a role in childbirth, lactation and attachment (Donaldson and Young, 2008; Yang et al., 2013), has been a focus of research on the causes of suicidal ideation and behavior. Clinical trials testing intranasal oxytocin administration in human subjects have substantiated oxytocin's role in prosocial behavior such as social cognition (Bartz et al., 2010; Domes et al., 2007; Kirsch et al., 2005), trust (Kosfeld et al., 2005; Mikolajczak et al., 2010; Theodoridou et al., 2009), generosity (Zak et al., 2007) and attachment (Bernaerts et al., 2017). Of note, higher levels of oxytocin have also been associated with negative interpersonal outcomes, such as derogation and defensive aggression toward an outgroup (De Dreu et al., 2011, 2010), envy and gloating (Shamay-Tsoory et al., 2009) and aggression toward a romantic partner (DeWall et al., 2014), suggesting that an excess may be deleterious.

In light of these complex findings, McQuaid et al. (2016, 2013) proposed a social sensitivity hypothesis, suggesting that oxytocin heightens response to social stimuli, regardless of stimulus valence. This also means that genetic associations may be the same for both negative and positive responses in a social context. A single nucleotide polymorphism (SNP) of the oxytocin receptor (*OXTR*) gene, rs53576, which involves a guanine (G) to adenine (A) substitution, has been studied in relation to this hypothesis. A-carrier genotypes are associated with

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decreased maternal sensitivity (Bakermans-Kranenburg and van Ijzendoorn, 2008), decreased empathy, increased stress reactivity (Rodrigues et al., 2009), lower levels of optimism, mastery, and self-esteem (Saphire-Bernstein et al., 2011), and autism (Wu et al., 2005). For this reason, the A allele of rs53576 has generally been considered the risk allele. GG homozygotes, however, have demonstrated a higher sensitivity to social exclusion (McQuaid et al., 2015), and among individuals who have experienced childhood maltreatment, the G allele is associated with increased depressive symptoms (McQuaid et al., 2013), increased emotion dysregulation (Bradley et al., 2011), and lower perceived social support (Hostinar et al., 2014). Individuals with the G allele may be more sensitive and less resilient in the face of negative life events, making the development of psychopathology more likely.

Polymorphisms of *CD38*, a gene for a transmembrane receptor regulating oxytocin secretion, may also interact with environmental factors to produce negative affective responses. The rs3796863 SNP, which involves a cytosine (C) to adenine (A) substitution, has been studied, again with complex findings. The C allele has been found to be associated with less parental touch (Feldman et al., 2012), fewer maternal interactions with their infants (Feldman et al., 2013), slower visual processing of social stimuli (Sauer et al., 2012) and autism (Lerer et al., 2010; Munesue et al., 2010). In contrast, others found the A allele to be associated with greater negative perceptions of parental and peer interactions (McInnis et al., 2017; McQuaid et al., 2016), as well as more depression and suicidal ideation (McQuaid et al., 2016). Furthermore, A-allele carriers experiencing chronic interpersonal stress were found more likely than CC homozygotes to exhibit symptoms of social anxiety and depression (Tabak et al., 2016). Moreover, past trauma was found to interact with genotype to predict suicidal ideation severity, such that suicidal ideation was most severe among AA homozygotes with a history of trauma (McQuaid et al., 2016). Thus, both C and A alleles have been associated with risk phenotypes.

Important to the social sensitivity hypothesis is the relationship between genotype and oxytocin levels. The A allele of the rs3796863 SNP has been found to be associated with higher plasma oxytocin (Feldman et al., 2012). Higher oxytocin levels in A-carriers may increase sensitivity to social stimuli, which may increase risk for depression or suicidal ideation and behavior in A-carriers with a history of negative life events or strained social relationships. A similar mechanism may involve the rs53576 SNP, although the effect of rs53576 genotype on plasma oxytocin is uncertain. One study found no relationship (Parker et al., 2014), while another found lower oxytocin levels in rs53576 GG participants (Moons et al., 2014). One possibility is that GG individuals may compensate for lower oxytocin levels via increased *OXTR* transcription related to the G allele (Reiner et al., 2015).

In light of this evidence that rs53576 and rs3796863 genotypes have complex relationships with depression and suicidal ideation, we explored their associations with suicide *attempt* and related risk phenotypes. We hypothesized that the G allele of rs53576 and the A allele of rs3796863 would be associated with lifetime suicide attempt history, as well as greater severity of depression and suicidal ideation. In line with the social sensitivity hypothesis, we explored whether the relationship between genotype and attempt history was more pronounced in individuals with a history of abuse or insecure attachment. Sex and mood disorder diagnosis were also tested as potential moderators, in light of evidence that oxytocin regulation may differ by sex (Dumais and Veenema, 2016; Feldman et al., 2010) and MDD versus BD diagnosis (Lien et al., 2017). Additionally, given the link between genetic load and earlier age of onset (Mendlewicz, 1979), we explored the relationship between genotype and age of the first major depressive episode (MDE). Finally, since aggression, hostility, and impulsivity have been implicated in suicide attempt risk (Mann et al., 1999; van Heeringen and Mann, 2014), we tested associations between these traits and genotype.

2. Methods

2.1. Study sample

The sample included 236 subjects (54.7% female) participating in mood disorder studies at New York State Psychiatric Institute-Columbia University Medical Center. The age of the sample ranged from 20 to 70 years, with a mean of 40 (SD = 12.4). The sample was limited to Caucasians to reduce the potential effect of racial stratification by genotype. Of the total sample, 161 had a DSM-IV diagnosis of major depressive disorder (MDD) and 75 had bipolar disorder (BD). One hundred and three (43.6%) subjects had made at least one lifetime suicide attempt, and 58 of these attempters (56.3%) were female. All patients were in a current MDE at baseline assessment. The study was approved by the Institutional Review Board at the New York State Psychiatric Institute and was conducted in compliance with the standards established in the Declaration of Helsinki. After complete study description, written informed consent was obtained from all participants.

2.2. Measures

Baseline Axis I diagnoses were determined using the structured clinical interview for DSM-IV patient edition (SCID I; Spitzer et al., 1990). The 17-item Hamilton depression rating scale (HDRS-17; Hamilton, 1960) and 21-item beck depression inventory (BDI; Beck et al., 1961) were used to measure depression severity at baseline. Suicidal ideation at baseline and two weeks prior to baseline was measured using the 19-item scale of suicidal ideation (SSI; Beck et al., 1979), which assesses passive and active ideation as well as preparatory behaviors. For baseline and two weeks pre-baseline time-points, a dichotomous suicidal ideation variable was created: ideation absent (SSI = 0) or present (SSI > 0). Suicide attempt history was assessed with the Columbia Suicide History Form (Oquendo et al., 2003). Raters were psychologists with a master's degree or PhD. Weekly reliability monitoring used videotaped assessments. Intra-class correlation coefficients (ICC) for key clinical ratings included: (SCID I) ICC = 0.94, (HDRS-17) ICC = 0.96, (SSI) ICC = 0.98. Aggression, hostility, and impulsivity were assessed using the Brown-Goodwin aggression inventory (Brown et al., 1979), Buss-Durkee hostility inventory (Buss and Durkee, 1957), and Barratt impulsivity scale (Barratt, 1965). Anxious and avoidant attachment styles were assessed using the 13-item adult attachment scale (AAS; Simpson, 1990), a self-report measure that asks subjects to respond to a series of statements regarding “how you usually feel toward your romantic partners”. To assess abuse history, subjects were asked whether they had experienced any physical and/or sexual abuse during their lifetime.

2.3. Genotyping

DNA was extracted from the peripheral blood mononuclear cell (PBMC) fraction using the FlexiGene DNA kit, (Qiagen, Hilden, Germany). The rs53576 and rs3796863 polymorphisms were characterized using a standard polymerase chain reaction (PCR). The restriction fragment length polymorphism (RFLP) method was used to determine the genotype. PCR was carried out in a 20 µl volume in a BioRad T100 Thermocycler (BioRad, CA, USA) using the HotStarTaq Plus Master Mix Kit (Qiagen, Hildem, Germany) with initial heating at 95 °C for 5 min. Thirty cycles, consisting of 30 secs at 95 °C, 40 s at 58 °C, and 40 s at 72 °C, were followed by a final extension step at 72 °C for 4 min. Primer sequences for the rs53576 polymorphism were forward: 5′-ATCCTGTCCAAGCTTCTCCT-3′ and reverse: 5′-AGGCCTGGTT TGAACTGTTT-3′. The 220 bp-long PCR product was digested with *Bam*HI (NE Biolabs, MA, USA). RFLP profiles were identified and visualized by 2% agarose gel electrophoresis. For the rs3796863 polymorphism, primer sequences were forward: 5′-ACAAGGTGCACAGACC