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Research paper

Genetic variants in oxytocin receptor gene (*OXTR*) and childhood physical abuse collaborate to modify the risk of aggression in chinese adolescents

Yanmei Zhang, Chunxia Wu, Hongjuan Chang, Qiuge Yan, Linguo Wu, Shanshan Yuan, Jingjing Xiang, Wen Hao, Yizhen Yu*

Department of Child, Adolescence and Woman Health Care, School of Public Health, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China

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ABSTRACT

Background: Accumulating evidence suggests that genetic and environmental factors may influence aggression susceptibility. However, the etiology of aggressive behavior remains unknown. Compared to some extensively studied candidate genes of aggression, very little is known about the *OXTR* gene. The objective of this study was to determine whether *OXTR* genetic variants were associated with aggression risk and whether these polymorphisms showed interactive effects with childhood maltreatment on aggression in Chinese adolescents.

Methods: A total of 996 participants including 488 cases and 488 controls were selected in our study. Aggression, childhood maltreatment were measured by self-reported questionnaire. Buccal cells were collected. Genotyping was performed using SNPscan. Logistic regressions were used to estimate both main effects of *OXTR* polymorphisms and the interactive effects with childhood maltreatment on aggressive behavior.

Results: Participants who carried the rs237885 TT genotypes in *OXTR* had a higher risk of aggression compared to those who carried GG or GT genotypes under the recessive model (OR = 1.40, 95% CI, 1.04–1.89) after controlling for potential confounders. In addition, we also found that the polymorphism had a synergic additive interaction with childhood physical abuse on the aggression risk.

Limitations: The subjects in the present study were only males, thus our findings and conclusions could not be generalized to females.

Conclusions: The present study provides evidence that *OXTR* genetic variants may contribute to aggression susceptibility. Moreover, this is the first study reporting significant interactive effects of *OXTR* polymorphism and childhood physical abuse on aggressive behavior in Chinese adolescents.

1. Introduction

Aggressive and violent behavior is a major cause of morbidity and mortality, and has been estimated to account for 1.5 million deaths annually, with an even larger number of nonfatal victims (Organization, 2007). Moreover, the number of deaths and nonfatal victims is likely to increase in the future because of inadequate control of aggressive behavior. Therefore, aggression has an enormous economic and social burden, highlighting the need for a better understanding of the underlying biological basis to enable the development of improved intervention strategies (Mcguire, 2008).

During recent decades, a considerable body of evidence based on twin and adoption studies has accumulated regarding the genetic and environmental effects on human aggression (Tuvblad and Baker, 2011). The findings suggest that around 50% of the variance can be ascribed to genetic factors, while the remaining 50% is explained by environmental factors (Tuvblad and Baker, 2011). Great efforts have been made to elucidate the possible genetic background of aggressive behavior, including investigations of the associations between polymorphisms in monoamine oxidase A gene (*MAOA*) (Antypa et al., 2013; Armstrong et al., 2014), catechol-O-methyltransferase gene (*COMT*) (Albaugh et al., 2010; Hirata et al., 2013), serotonin transporter gene (*5HTT*) (Åslund et al., 2013; Gyurak et al., 2013) and dopamine receptor D4 gene (*DRD4*) (Buchmann et al., 2014; Dmitrieva et al., 2011) and aggression risk. However, very few studies have investigated the link between the candidate gene *OXTR* and aggression susceptibility, particularly among Chinese adolescents. Additionally, previous studies suggested that boys were more aggressive than girls (Das and Tripathy, 2015; Salmivalli and Kaukiainen, 2004). And given the availability of participants' buccal cells and the restricted funds for subsequent genotyping, only male adolescents were included in the present study.

Abbreviations: PHY, physical aggression; VER, verbal aggression; ANG, anger; HOS, hostility; IND, indirect aggression; CTQ, childhood trauma questionnaire

* Correspondence to: School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Hangkong Road 13, Wuhan 430030, Hubei, China.
E-mail address: yuyizhen650@163.com (Y. Yu).

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Oxytocin is a neuropeptide synthesized in the hypothalamus that plays crucial roles in lactation and parturition (Rao et al., 1992), as well as in prosocial behaviors as both a neurotransmitter and a neuromodulator. In humans, oxytocin has been associated with complex social behavior and emotional states, such as generosity, trust, facial emotion recognition, and emotional regulation (Heinrichs and Domes, 2008; Meyerlindenberg et al., 2011; Neumann, 2008), all of which can be partially damaged in aggressive subjects (Meyerlindenberg et al., 2011). Lee et al. found that the levels of oxytocin in cerebrospinal fluid were inversely associated with a life history of aggressive behavior (Lee et al., 2009), Besides, Fetissov and colleagues (Fetissov et al., 2006) reported that aggressive male subjects had higher levels of autoantibodies reactive for oxytocin compared with controls suggesting that hypo-oxytocinergic function may contribute to aggressive behavior. Studies involving the exogenous administration of oxytocin reported the amplified prosocial behaviors such as trust (Kosfeld et al., 2005; Mikolajczak et al., 2010), further indicating the existence of a negative association between oxytocin and aggressive behavior (Tauber, 2011). Moreover, oxytocin reduces neural activation of the amygdala in the limbic brain region especially as a response to angry faces (Kirsch et al., 2005).

These findings suggest that oxytocin dysregulation induced by genetic variants may disrupt prosocial behaviors and predispose an individual to aggressive and antisocial behavior. However, contrary to the above results, a recent study by De Dreu et al.(De Dreu et al., 2010) showed that oxytocin could increase defensive, but not offensive, aggression toward competing out-groups. A plausible explanation may be that oxytocin increases cooperation with trust-worthy individuals but decreases such behavior in competitive situations (Bartz et al., 2011). On the other hand, evidence from animal research also suggests that oxytocin is involved in aggressive behavior (Devries and Nelson, 1997; Harmon et al., 2002; Lubin et al., 2003; Matzuk et al., 2005; Ragnauth et al., 2005; Winslow and Insel, 2002).

It is possible that the effects of oxytocin are modulated by the expression of *OXTR*. Malik et al. (Malik et al., 2012) found an association between *OXTR* polymorphisms and extreme, persistent and pervasive aggressive behavior. However, Johansson (Johansson et al., 2012a) and colleagues found no main effects of *OXTR* polymorphisms on aggressive behavior. With regard to the controversy, the association between *OXTR* polymorphisms and aggression remains to be clarified.

Regarding the role of environmental factors on aggression, a number of studies focused on the associations between family adversity, violent media exposure, alcohol consumption and maltreatment, and aggression susceptibility (Craig, 2007; Craig and Halton, 2009; Tuvblad et al., 2009). However, the findings are inconsistent, and only alcohol consumption was reported to interact with *OXTR* polymorphisms on aggression susceptibility (Johansson et al., 2012b). In the present study, we focus on the childhood maltreatment.

Therefore, the aim of the current study was to determine whether *OXTR* genetic variants were associated with aggression risk, and whether these polymorphisms showed interactive effects with childhood maltreatment on aggressive behavior in Chinese adolescents.

2. Materials and methods

2.1. Study population

A total of 976 male subjects (488 aggression cases and 488 controls) from the ongoing Tongji aggression study project, participated in the present study. This study was conducted from September 2014 to April 2016 in selected schools from Xiaogan, Yingshan, and Wuhan cities in Hubei Province, China.

A structured questionnaire was used to collect information on basic demographic characteristics, life styles, history of childhood maltreatment, and other related information by a group of trained interviewers, who explained the procedure and purpose of this study. The self-administered survey was anonymous, and was completed in classrooms during a 30–40 min period. All participants were told that there were no so-called correct or incorrect answers, that all questions should be answered honestly and accurately, and that their answers would be kept confidential and used for scientific research only. Subjects with chronic medical illness or a diagnosis of schizophrenia or autism based on clinical records were excluded from the study.

2.2. Ethics statement

Written informed consent was obtained from all participants and their parents or guardians. This study was approved by the Ethics Committee of the School of Public Health, Tongji Medical College, Huazhong University of Science and Technology. All the methods in this study were carried out in accordance with the approved guidelines.

2.3. Assessment of aggression

The Chinese version of Buss and Warren's Aggression Questionnaire (BWAQ) was administered to assess aggression (Buss and Warren, 2000; Maxwell, 2007). This self-reported questionnaire consisted of 34 items, which were answered on a 5-point Likert scale ranging from 1 (not at all like me) to 5 (completely like me). It measured five dimensions related to aggression: physical aggression (PHY), verbal aggression (VER), anger (ANG), hostility (HOS), and indirect aggression (IND), with the higher scores of each dimension reflecting corresponding higher levels of aggression. According to the interpretation of BWAQ, the related aggression scores were classified into seven grades 1–7): very low (≤ 29 *T*), low (30*T*–39 *T*), low average(40*T*–44 *T*), average (45*T*–55 *T*), high average (56*T*–59 *T*), high (60*T*–69 *T*), and very high (≥ 70 *T*) respectively. Participants were recognized as aggression cases if their total *T* scores classified into the sixth or seventh grade (≥ 60 *T*). The same number of participants with BWAQ scores that below 60 T were selected as control group from the ongoing Tongji aggression study project. The BWAQ has been proven to have good psychometric properties (Maxwell, 2008) (internal reliability: PHY = 0.81, VER = 0.71, ANG = 0.64, HOS = 0.61, and IND = 0.62). The internal consistency as reflected by the overall Cronbach coefficient alpha of the 34 items in the present study was 0.94, and the internal consistency for each subscale was 0.87, 0.62, 0.71, 0.75, and 0.78, respectively.

2.4. Assessment of childhood maltreatment

All subjects completed the short version of the Childhood Trauma Questionnaire (CTQ)(Bernstein and Fink, 1998; Bernstein et al., 2003), a 28-item retrospective self-report questionnaire. In the CTQ, the child maltreatment domains of physical, sexual, and emotional abuse, and physical and emotional neglect are each assessed by five items that participants rate on a 5-point, Likert-type scale ranging from “never true” to “very often true” according to the frequency with which each event occurred. Physical abuse was defined as bodily assaults on a child by an adult or older person that poses a risk for or results in injury; sexual abuse as sexual contact, or conduct between a child younger than 18 years of age and an adult or older person; emotional abuse as “verbal assaults on a child's sense of worth or well-being, or any humiliating, demeaning, or threatening behavior directed toward a child by an adult or older person”; physical neglect as failure of caregivers to provide a child's basic physical needs including food, shelter, clothing, safety, and health care; and emotional neglect as the failure of caretakers to provide basic psychological and emotional needs including love, belonging, nurturance, and support (Bernstein et al., 1994). Scores across the five child maltreatment domains were summed to achieve a total CTQ score; the five subscale scores permitted assessments to be made for effects in each of the five abuse and neglect domains. Internal consistency has previously ranged from 0.76 to 0.92 (Bernstein et al., 1994; Bernstein et al., 2003; Buchmann et al., 2014; Mezzacappa et al.,