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Research article

Association between oxytocin and receptor genetic polymorphisms and aggression in a northern Chinese Han population with alcohol dependence

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HIGHLIGHTS

- Rs6133010 in the OXTR gene was associated with AD related aggression in northern Chinese Han population.
- The genotype GG of rs6133010 carriers in AD group had significant anger aggression.
- The 3-loci interaction combination of rs6133010AG, rs2254298AG and rs53576AA increases risk for AD.

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ABSTRACT

Objective: Alcohol dependence (AD) is a common chronic brain disorder precipitated by complex interactions between biological, genetic, and environmental risk factors. Aggression often occurs in the context of AD. Previous studies have shown that Oxytocin (OXT) and OXT receptor (OXTR) are involved in the regulation of aggression. The present study investigated whether variations and interactions of OXT and OXTR genes were associated with AD-related aggression in a genetically homogeneous northern Chinese Han population.

Methods: Three hundred and twenty-four male AD patients and 510 male healthy controls (HCs) were recruited. A Chinese version of the Buss-Perry Aggression Questionnaire was used as a subjective measurement of aggressive behavior. Three variations, rs2254298, rs53576, and rs6133010 were genotyped using TaqMan and ligase detection reaction for all subjects. Generalized Multifactor Dimensionality Reduction was used to detect interactions between genetic attributes and environmental attributes.

Results: The frequencies of alleles and genotypes of rs6133010 were significantly different between AD patients and HCs ($p < 0.001$). In HCs, the effect of genotype GG of rs53576 on hostility aggression was significantly stronger than that of genotype AA and AG ($p = 0.001$ and $p = 0.004$, respectively), and the subjects with the interaction combination of rs6133010AA × rs2254298GG × rs53576AG exhibited significant effect on physical aggression ($p = 0.0107$).

Abbreviation: OXT, oxytocin; OXTR, oxytocin receptor; CNS, central nervous system; SNP, single nucleotide polymorphism; AD, alcohol dependence; HCs, healthy controls; GMDR, Generalized Multifactor Dimensionality Reduction; BPAQ, the Buss-Perry Aggression Questionnaire.

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Conclusion: The present study found that rs6133010 in the OXT gene is associated with AD in the northern Chinese Han population. The polymorphisms of OXT/R may play a key role in the susceptibility of AD-related aggression.

1. Introduction

Alcohol dependence (AD) is a condition which involves prolonged alcohol craving caused by long-term, frequent drinking [39]. This diagnosis is used to describe an individual that is physically or psychologically dependent upon drinking alcohol. A previous study identified a link between aggression and alcohol use [22], and AD was found to be correlated with aggression [18]. Alcohol-related aggression shows large interindividual differences [4,20]. These results support the hypothesis that genetic variants may play an important effect in AD-related aggression.

Oxytocin (OXT) is synthesized in the hypothalamus [12] and plays a prosocial role in human and animal behavior [2], including maternal behavior, sexual behavior, social recognition and social contact [36]. OXT has been correlated with brain reward system regulation [35]. A few recent studies have suggested that OXT decreases alcohol use in rats and reduces symptoms of alcohol withdrawal and craving behavior in dependent patients during abstinence [6,7,38]. Cerebrospinal fluid OXT levels were inversely correlated with life history of aggression [27]. A previous study found that OXT administration leads to a broad range of changes in aggressive response, as measured by the point subtraction aggression paradigm [1]. The central actions of OXT are mediated via oxytocin receptors (OXTRs) that are found in the regions of the mammalian brain associated with the reward system [3]. **OXTRs were visualized in some regions of the amygdala and hypothalamus, the limbic and basal forebrain, olfactory nucleus and the anterior cingulate, the part of the brain that includes reward memory** [5,16]. Peripheral injections of an OXTR antagonist significantly reduce male-male and female-female aggression in a highly territorial finch, providing evidence that endogenous activation of OXTR promotes resident-intruder aggression [17]. Allelic variability of OXT pathway also impacts human social functions [15]. The polymorphisms of the OXT/R genes have been correlated with the modulation of social cognitive behavior [11].

The OXT gene is located on chromosome 20p13. Three polymorphisms were chosen from dbSNP (http://www.ncbi.nlm.nih.gov/SNP/). Rs6133010 is located in the OXT promoter region [45]. The association between OXTR variants and childhood-onset aggression was found in a study with highly aggressive children [31]. The OXTR gene is located on chromosome 3p25 and has 4 exons and 3 introns [23]. Two single nucleotide polymorphisms (SNPs) located in intron 3 of the OXTR gene, rs2254298 and rs53576, were found to be related to individual differences in empathy and prosocial behaviors [9,14]. It has been reported that rs2254298 is associated with sociability, amygdala volume and differential risk for psychiatric conditions including autism, depression and anxiety disorder, depending on the quality of early environmental experiences [9]. The SNP rs53576 is involved in differences of oxytocinergic functioning [34]. The rs53576 GG genotype has been found to be associated with general social phenotypes, psychological resources, higher empathy lower stress reactivity and a prosocial temperament [44]. In addition, there is evidence that the rs53576 G allele may contribute to the risk of emotional and behavioral problems by gene environment interaction [8,23].

Notably, little studies have been performed on the roles of OXT/R genetic polymorphisms in AD-related aggression. Taken together, the association of variations and interactions of OXT/R genes with AD-related aggression warrants further investigation. Therefore, the aim of this present study was to investigate the association between these 3 loci (rs2254298, rs53576 and rs6133010) and their interactions in AD-related aggression in a Chinese Han male population.

2. Experimental procedures

2.1. Subjects

A total of 324 male AD inpatients were recruited from the Psychiatric Hospitals in northern China. All of the patients met criteria for AD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). Participants without a history of other drug abuse or dependence, with the exception of nicotine, were included.

Five hundred and ten unrelated male healthy controls (HCs) from Inner Mongolia Autonomous Region were recruited. All of the HCs lacked a history of drug abuse or dependence, with the exception of nicotine. All participants with serious liver or kidney disease, or participants or first-degree relatives of participants that have serious mental illness, were excluded. Two skillful psychiatrists conducted the diagnoses. All of the staff were trained before starting this study.

2.2. Measurement of aggression

A Chinese version of the Buss-Perry Aggression Questionnaire (BPAQ) was used to measure aggressive behavior [10]. All of the subjects described their own patterns of aggression-related behavior, emotions, and attitudes by self-reporting [46]. The revised Chinese version 30-item BPAQ provides 5-subscale scores measuring physical aggression, verbal aggression, anger, hostility and indirect aggression [1]. Informed written consent was obtained from all subjects before study participation. **The BPAQ of inpatients was assessed in one week for the case of emotional stability**. This study was approved by the Peking University Institutional Review Board.

2.3. Genotyping

A salting-out method to extract genomic DNA with 5 ml peripheral blood was used [43]. Genotyping was performed for rs2254298, rs53576 and rs6133010 in a total of 834 subjects. The 3 SNPs in the OXT/R genes were genotyped using the 5'nuclease fluorescent TaqMan™ primer (Applied Biosystems, Foster City, CA). The protocol was performed in accordance with manufacturer's instructions. All of the laboratory procedures were carried out in a blind manner to case control status. The conditions of PCR were as follows: 50 °C for 2 min, 95 °C for 10 min, followed by 50 cycles of 95 °C for 15 s and 60 °C for 1 min **Ten percent of the DNA samples were duplicated randomly and tested, and no fault genotyping was found**.