Psychoneuroendocrinology 86 (2017) 45–52

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Oxytocin receptor gene polymorphisms exert a modulating effect on the onset age in patients with obsessive-compulsive disorder

Jee In Kang[a,b], Hae Won Kim[b,c], Chul Hoon Kim[d], Eun Hee Hwang[b], Se Joo Kim[a,b,*]

[a] Department of Psychiatry, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Department of Medical Education, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Department of Pharmacology, BK21 PLUS Project for Medical Science, Brain Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Genetic association study
Oxytocin
OXTR
Age at onset

ABSTRACT

The oxytocin receptor (*OXTR*) is a potential candidate in the pathophysiology of obsessive-compulsive disorder (OCD). The present study investigated the association between common single-nucleotide polymorphism (SNPs) of the *OXTR* gene and the affected status of OCD or distinct clinical subtypes of OCD including the age at onset and symptom dimensions. Ten SNPs of *OXTR* were examined in 615 patients with OCD and 581 healthy controls. Single-marker and haplotype-based association analyses were conducted. While *OXTR* variants were not associated with the affected status of OCD or its clinical symptom dimensions, rs2268493 (p = 0.00185) and rs13316193 (p = 0.00461) of the *OXTR* gene were associated with the age at onset in patients with OCD. In addition, in haplotype-based association analyses, there was a significant association between the *OXTR* gene and the onset age in patients with OCD. In particular, the G-C-G haplotype of rs2268493-rs2254298-rs11316193 and the T-G-A haplotype of rs237887-rs2268490-rs4686301 were positively associated with late-onset OCD. Our results suggest that common variants of *OXTR* may exert a modulating effect on the onset age in OCD pathophysiology. The potential involvement of the oxytocin system in the development and expression of OCD warrants further longitudinal research.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common and debilitating mental disorder characterised by maladaptive patterns of repetitive, inflexible thoughts and behaviours that cause severe distress and interfere with interpersonal functioning. Cognitive perspectives on OCD propose that the lack of cognitive flexibility is a key feature of OCD (Gruner and Pittenger, 2017). Psycho-dynamically, isolation of affect is a core defence of OCD, which allows patients to control intolerable emotions and aggression by disconnecting affective elements from thoughts or situations (Barth, 1990; Fenichel, 1945). However, the mechanisms underlying these cognitive and socio-emotional characteristics of OCD remain unclear.

It is well known that neurotransmitters such as serotonin and dopamine play major roles in the pathophysiology of OCD. However, beyond the serotonin and dopamine systems, increasing evidence suggests that the neuropeptides oxytocin and arginine vasopressin are also important in the pathophysiology of OCD (McDougle et al., 1999). Oxytocin and arginine vasopressin are known to have neuromodulatory effects on brain function and are thought to be involved in cognitive and socio-emotional development (Bachner-Melman and Ebstein, 2014; Carter, 2003; Neumann, 2008). In particular, the oxytocin system is also reported to interact anatomically and functionally with the serotonin and dopamine systems (Baskerville and Douglas, 2010; Dolen et al., 2013; Lefevre et al., 2017). Growing evidence shows that coordinated actions of oxytocin and serotonin in the nucleus accumbens affect social rewards (Dolen et al., 2013), and interactions of oxytocin and dopamine partially mediate social behaviors via their integrated brain circuits (Baskerville and Douglas, 2010). A recent study in non-human primates showed that oxytocin administration influences serotoninergic neurotransmission by provoking 5-HT release and availability of 5-HT_{1A}R receptors in limbic regions (Lefevre et al., 2017). In addition, there is supporting evidence implicating the involvement of oxytocin in OCD. In animal studies, oxytocin has been shown to exaggerate grooming behaviours, which is considered an experimental model of compulsion (Marroni et al., 2007; Van Wimersma Greidanus et al., 1990). Human studies also support that oxytocin may play a crucial role in OCD. For example, the cerebrospinal fluid oxytocin level was higher in adults with non-tic-related OCD and was correlated with symptom severity of OCD (Leckman et al., 1994). Similarly, another

* Corresponding author at: Department of Psychiatry, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
E-mail address: kimsejoo@yuhs.ac (S.J. Kim).

http://dx.doi.org/10.1016/j.psyneuen.2017.09.011
Received 27 April 2017; Received in revised form 23 August 2017; Accepted 6 September 2017

study showed that the plasma oxytocin level was higher in patients with OCD than it was in healthy controls (Marazziti et al., 2015). In addition, the baseline oxytocin level was reportedly negatively correlated with the age at onset in patients with OCD (Humble et al., 2013). Although the therapeutic effects of oxytocin on OC symptoms remain controversial (den Boer and Westenberg, 1992; Epperson et al., 1996), one study reported improvements in OC symptoms after treatment with intranasal oxytocin (Ansseau et al., 1987). Collectively, these findings suggest that the oxytocin system may be involved in the aetiology and expression of OCD.

Since the actions of oxytocin are transduced via oxytocin receptors (OXTR), *OXTR* is an attractive candidate gene for OCD. OXTRs are present in certain brain areas including the cortex, limbic system, basal ganglia, thalamus, and hypothalamus, which are all areas that have been implicated in the aetiology of OCD (Rasmussen et al., 2013). Additionally, a number of genetic studies on the *OXTR* gene have been conducted to determine its role on human sociality and various social psychopathologies (Feldman et al., 2016). In particular, several *OXTR* gene variants are considered to be associated with autism spectrum disorder (ASD) (LoParo and Waldman, 2015). Furthermore, clinical trials of ASD have shown that *OXTR* gene variants may contribute to the differential treatment responses that have been observed following oxytocin administration in patients with autism (Kosaka et al., 2016; Watanabe et al., 2017). However, few genetic studies have investigated the influence of *OXTR* on OCD. To the best of our knowledge, only one epigenetic study has reported an association between the *OXTR* gene and OCD (Cappi et al., 2016).

Therefore, the aim of the present study was to investigate the association between common SNPs of the *OXTR* gene and OCD. Because OCD is a heterogeneous condition (Miguel et al., 2005), we also stratified patients with OCD into more homogeneous subtypes according to the age at onset and OC symptom dimensions.

2. Material and methods

2.1. Subjects

A total of 615 patients with OCD (ages 19–65) and 581 healthy controls (ages 19–51) participated in this study. Socio-demographic and clinical characteristics of the subjects are presented in Table 1. All of the patients were primarily diagnosed with OCD by a trained psychiatrist who used the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Axis I disorders (First et al., 1996). Patients with a lifetime history of psychotic symptoms, history of substance abuse or dependence in the preceding 6 months, or severe organic or neurologic disorders were excluded. Patients with comorbid DSM-IV Axis I disorders were not excluded as long as OCD was the primary diagnosis. Patients with OCD were further classified into early onset (age at onset $\leq$17 years) and late-onset ($>$ 17 years) OCD depending on the age at which the OC symptoms first occurred as remembered by the patients or family members (Wang et al., 2012).

Sex-matched healthy control participants were recruited through advertisements. Controls with a lifetime history of DSM-IV Axis I disorders or neurological disorders were excluded. The ethnic backgrounds of all participants were ascertained through self-reports and only those who were ethnically Korean were enrolled. All participants provided written informed consent, and this study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea.

2.2. Measures

The clinical symptoms and severity of OCD symptoms were assessed using the Yale-Brown obsessive-compulsive scale (Y-BOCS) (Goodman et al., 1991). The Y-BOCS symptom checklist (Goodman et al., 1991) was employed to measure the patients' scores in the following four dimensions of OC symptoms, as identified by Bloch et al. in their meta-analysis (Bloch et al., 2008): (1) symmetry – symmetry obsessions and repeating, ordering, and counting compulsions; (2) forbidden thoughts – aggressive, sexual, religious, and somatic obsessions and checking compulsions; (3) cleaning – contamination obsessions and cleaning compulsions; and (4) hoarding – hoarding obsessions and compulsions. The presence of a dimension was determined based on the current or lifetime history of one or more symptoms in each category.

2.3. SNP selection

Among the *OXTR* SNPs, 10 SNPs were selected based on the literature associating *OXTR* genes with various social behaviours, minor

Table 1
Socio-demographic and clinical characteristics of the study sample.

Variable	Early onset OCD (n = 339)	Adult onset OCD (n = 276)	OCD (n = 615)	Controls (n = 581)	P value
Age, years	25.16 ± 6.99	35.80 ± 11.56			< 0.001
(age range)	(19–61)	(19–65)	29.94 ± 10.71	22.47 ± 3.43	< 0.001
Male/Female, *n*	253/86	145/131			< 0.001
			398/217	315/266	< 0.001
Onset age of OCD, years	12.86 ± 3.12	25.56 ± 9.27	18.56 ± 9.16		< 0.001
(age range)	(3–17)	(18–64)			
Illness duration, years	12.30 ± 7.29	10.24 ± 9.35	11.37 ± 8.33		0.003
Baseline Y-BOCS score					
Total	25.00 ± 6.27	24.99 ± 5.67	24.99 ± 6.00		0.976
Obsessions	12.67 ± 3.19	12.68 ± 2.86	12.68 ± 3.04		0.961
Compulsions	12.32 ± 3.62	12.27 ± 3.28	12.30 ± 3.47		0.851
Basal MADRS score	18.95 ± 8.91	18.11 ± 8.39	18.57 ± 8.69		0.231
Comorbid diagnosis, *n* (%)					
Major depression	39 (11.5)	40 (14.5)	79 (12.8)		0.271
Tic	24 (7.1)	3 (1.1)	27 (4.4)		< 0.001
Others	42 (12.4)	28 (10.3)	70 (11.4)		0.410
Symptom dimensions, present, *n* (%)					
Symmetry	291 (85.8)	185 (67.0)	476 (77.4)		< 0.001
Forbidden thoughts	315 (92.9)	234 (84.8)	549 (89.3)		0.001
Cleaning	274 (80.8)	197 (71.4)	471 (76.6)		0.006
Hoarding	143 (42.2)	72 (26.1)	215 (35.0)		< 0.001

OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown obsessive-compulsive scale; MADRS, Montgomery-Åsberg depression rating scale.