

Mutation analysis of oxytocin gene in individuals with adult separation anxiety

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Abstract

Individuals with a diagnosis of adult separation anxiety (ASAD) have extreme anxiety about separations, actual or imagined, from major attachment figures. ASAD might represent a psychological/behavioral model for research probably involving a dysregulation of those neurobiological mechanisms of attachment, in particular central oxytocin (OT), described in numerous animal studies. As experimental strategy, we chose the nucleotidic sequencing of the human OT gene of patients with ASAD to evaluate whether OT mutations were related to potential alteration of its production. With this aim, mutation scanning of proximal promoter and untranslated and coding regions of the OT gene was carried out in 36 patients with ASAD, 14 patients without ASAD, and 26 controls. No mutations were found in promoter and coding regions of the OT gene in our population. One rare 3'UTR single nucleotide variant (rs17339677) and one intron 2 molecular variant (rs34097556), which showed a high frequency, were evidenced. There was no significant difference in the genotype distribution of this intron 2 polymorphism between patients and healthy individuals. Further research is needed to investigate the association between ASAD and OT peptide and receptor polymorphisms.

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1. Introduction

Oxytocin (OT) is a neuropeptide synthesized in the supraoptic and para-ventricular nuclei of the hypothalamus. Parallel to its well-known peripheral effects, OT is also released centrally from hypothalamic and extra-

hypothalamic neuronal groups to a variety of brain areas, including the hippocampus, amygdala, lateral septum, caudate and anterior olfactory nucleus. OT is synthesized as part of a larger precursor molecule containing, in addition to the OT domain, the neurophysin domain, which is involved in the binding of OT during axonal transport. In the secretory granules, processing of the prohormone takes place, and upon stimulation of nerve terminals, processing products are released (de Bree,

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2000). The human OT gene is composed of three exons and two introns: the first exon encodes the 19-amino-acid signal sequence, the nonapeptide hormone, a tripeptide processing peptide (GKR), and the first nine amino acids of neurophysin. The second exon encodes the central part of neurophysin (10–76) while the third exon encodes the COOH-terminal region of neurophysin (residues 77–94) (Sausville et al., 1985).

OT central effects are complex and include an involvement in social affiliation (Carter, 1998), sexual and maternal–infant bonding (Insel et al., 1997), anxiety (McCarthy et al., 1996) and mood (Bjorkstrand and Uvnas-Moberg, 1996). Recently, our knowledge of OT central effects has been extended by the development of OT knockout (OTKO) mice and rat (Winslow and Insel, 2002). Adult OTKO mice have been tested in an elevated plus maze, a behavioral test of anxiety, or exposed to psychogenic stressors. In these studies it has been evidenced that OTKO mice not only displayed more anxiety-related behavior (Mantella et al., 2003; Amico et al., 2004), but also released more corticosterone after a psychogenic stressor and manifested greater stress-induced hyperthermia, compared with wild type mice (Amico et al., 2004). In addition, it has been observed that these mice failed to recognize familiar conspecifics after repeated social encounters and showed elevated aggressive behavior (Ferguson et al., 2000; Winslow et al., 2000; Takayanagi et al., 2005). Thus, it has been proposed that this neuropeptide may act as a neuromodulator and may come into play when the brain is trying to adapt to various types of challenges. In particular, it has been suggested that its production, upon stressor exposure, can be beneficial to the individual serving to attenuate the response to psychogenic provocation (Amico et al., 2004). Pharmacological studies suggested that exogenously administered OT attenuates stress, anxiety and might promote positive social interaction (Carter, 1998; Pedersen and Boccia, 2002; McCarthy and Altemus, 1997). For these considerations, a long-term alteration of central OT production could explain the wide spectrum of psychopathologic effects, characterized by dysregulated responses to stress. For example, alterations of OT levels have been found in patients with depression, autism, and obsessive-compulsive disorder (Anderberg and Uvnas-Moberg, 2000; Frasch et al., 1995; Pitts et al., 1995; van Londen et al., 1997; Modahl et al., 1998). In this study, we were interested in investigating whether OT could be implicated in separation anxiety. Separation anxiety disorder is a well-established diagnostic category in the DSM-IV-TR only for childhood. However, recent epidemiological data show that

this disorder may also occur during adulthood with a lifetime prevalence in the general population of 6.6% (Shear et al., 2006). Adult separation anxiety (ASAD) is characterized by extreme anxiety about separations, actual or imagined, from major attachment figures.

Because measurement of peripheral OT level might not be correlated with its central functioning, we chose the nucleotidic sequencing of the human OT gene of patients with ASAD to evaluate whether OT mutations were related to potential alteration of its production. The finding of numerous mutations located in the part encoding the signal sequence or the neurophysin of the structurally related antidiuretic vasopressin gene led us to hypothesise these regions as being more likely candidate regions with respect to that encoding for OT. Of course, we could not rule out the possibility that potential mutations could be localized in untranslated regions or in regions implicated in transcriptional control.

2. Methods

2.1. Subjects and psychometric evaluation

The study sample was recruited at the outpatients clinic of the Department of Psychiatry, University of Pisa between April 2006 and March 2007. Subjects were assessed with the SCID-I for principal diagnosis and for the presence of Axis I comorbidity (Spitzer et al., 1990). A total of 50 patients were included in the study. Of these, 20 had a DSM-IV lifetime diagnosis of major depressive disorder, 13 of bipolar disorder type I or type II, 7 of obsessive-compulsive disorder, and 10 of panic disorder. Each individual was also evaluated by two scales for separation anxiety: (1) the Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS), which comprises a childhood section (SCI-SAS-C) and an adulthood section (SCI-SAS-A), respectively (Cyrnowski et al., 2002); and (2) the Adult Separation Anxiety Checklist (ASA-27) (Manicavasagar et al., 2003). The presence or absence of DSM-IV defined separation anxiety disorder and the extent of separation anxiety symptoms reported during childhood and adulthood were determined retrospectively using the SCI-SAS interview. The eight separation anxiety disorder criteria were rated for both childhood and adulthood time frames, scored as 0 (not at all), 1 (sometimes), 2 (often) or ? (do not recall). In keeping with the DSM-IV guidelines, endorsement of three or more of the eight criterion symptoms (symptoms rated as ‘2’ or ‘often’) was used as a threshold to determine categorical (yes/no) diagnosis of separation anxiety disorder in childhood and adulthood. In addition, criterion B

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