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Oxytocin receptor polymorphisms and adult attachment style in patients with depression

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Summary Much evidence of an association between specific attachment styles and depression prompted us to investigate, in depressive disorders, the potential role of polymorphisms within the gene encoding the receptor of the main neurohormone involved in attachment processes, oxytocin. For this purpose, two single nucleotide polymorphisms (SNPs), 6930G>A (rs53576) and 9073G>A (rs2254298), within the oxytocin receptor gene (*OXTR*), were studied in a cohort of 185 patients with major depression (50.3%) or bipolar I or II disorders (49.7%) and 192 matched healthy controls. A positive association between the GG genotype of *OXTR* SNPs (6930G>A or 9073G>A) and unipolar depression was demonstrated. In this group, GG individuals showed high scores on Attachment Style Questionnaire factors that have been previously associated with depression. Moreover, the GG genotype was also associated with high levels of adult separation anxiety. These findings support the involvement of the oxytocinergic system in the mechanisms that underlie depression and specific adult attachment styles.

1. Introduction

Depressive episodes are thought to result from the interplay of multiple genes interacting with environmental factors (Swaab et al., 2005; Grippo et al., 2007).

Several authors have suggested the involvement of the neuropeptide oxytocin (OXT) in depression based on evaluation of its levels in plasmatic/cerebrospinal fluid and of OXT transcripts in post mortem tissues (Zetzsche et al., 1996;

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Purba et al., 1996; Van Londen et al., 1997; Bell et al., 2006; Scantamburlo et al., 2007; Cyranowski et al., 2008; Wang et al., 2008). The traditional view of OXT as an endocrine hormone acting on peripheral organs (i.e., to induce labor and milk ejection) has been revised such that this neuropeptide is now considered to be a neurotransmitter or neuromodulator with central actions in the limbic system, the forebrain and the autonomic centers of the brainstem. Oxytocin plays a role in a variety of central functions, such as sexual behavior, maternal behavior, affiliation, social memory, satiety and stress responsiveness. In particular, there is strong evidence concerning the involvement of OXT in attachment processes in animals (Insel, 1997, 1992) and, despite a limited amount of detailed experimental data, some evidence to support similar behavioral effects in humans as well (Carter, 1998; Uvnäs-Moberg, 1998; Donaldson and Young, 2008). In a number of clinical studies, an association between specific adult attachment styles and depression has been found (Carnelley et al., 1994; Murphy and Bates, 1997; Mickelson et al., 1997; Bifulco et al., 2002; Shaver et al., 2005). Specifically, attachment anxiety, which concerns apprehension over rejection and abandonment, has been associated with depression (Carnelley et al., 1994; Murphy and Bates, 1997; Mickelson et al., 1997; Bifulco et al., 2002; Shaver et al., 2005). Attachment anxiety represents one of the two primary dimensions involved in self-report measures of adult attachment style (Bartholomew and Horowitz, 1991; Brennan et al., 1998). The second dimension, attachment avoidance, concerns the degree to which a person feels uncomfortable depending on and being emotionally close to others. Hypothesized explanations for the association between attachment anxiety and depression include anxious peoples' negative models of self (e.g., believing they are unlovable; Bartholomew and Horowitz, 1991), low self-esteem (Griffin and Bartholomew, 1994), self-criticism (Murphy and Bates, 1997) and dysfunctional attributions to partners' behavior that increase the likelihood of separation anxiety (Collins, 1996). In contrast, people high in avoidance generally invest less in relationships, are less upset when they end and are relatively low in commitment and relationship satisfaction (Mikulincer and Shaver, 2007).

Genetic factors have been reported to play a role in the development of depression (aan het Rot et al., 2009; Martinowich et al., 2009) without any reference to attachment styles. Genetic studies on attachment styles have also been performed (Carlson, 1998; Donnellan et al., 2008). These data, despite providing information about the possible contribution of genes to adult attachment style, rarely reveal which genes are involved. To the best of our knowledge, only polymorphisms of the D_2 and D_4 dopamine receptor genes and the $5HT_{2A}$ serotonin receptor gene have been associated with specific attachment styles (Van Ijzendoorn and Bakermans-Kranenburg, 2006; Gillath et al., 2008).

All these data together prompted us to focus in the present report on the OXT receptor (OXTR) gene as a possible candidate for genetic vulnerability to depression. For this aim, a comparison of genotype distributions of the two *OXTR* single nucleotide polymorphisms (SNPs), 6930G>A (rs53576) and 9073G>A (rs2254298), among patient groups with depression and healthy control group was performed. Moreover, associations between certain genotype groups and specific adult attachment styles were also investigated. To this end, we compared the scores on the five subscales of the Attachment Style Questionnaire among genotype groups.

2. Methods and materials

2.1. Subjects and psychometric evaluation

For the study, 185 patients referred to the clinics of the Department of Psychiatry at the University of Pisa for treatment of a depressive episode were recruited. All subjects were assessed with the SCID-I (First et al., 2002) to establish a DSM-IV Axis-I diagnosis and psychiatric comorbidity. The Hamilton Depression Rating Scale (Hamilton, 1960) and the Young Mania Rating Scale (Young et al., 1978) were used to assess the severity of depression and mania, respectively. Anxiety was assessed by the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959).

2.2. Attachment style evaluation

Patients were evaluated by the Attachment Style Questionnaire (ASQ) (Feeney et al., 1994). The ASQ is a 40-item self-report questionnaire with individual items being scored on a 6-point scale from 1 = totally disagree to 6 = totally agree. The ASQ includes five scales derived from principal components analysis: confidence (in self and others); discomfort with closeness; need for approval; preoccupation with relationships; and relationships as secondary (to achievement). *Confidence* (in self and others) reflects a secure attachment orientation.

The *Need for approval* scale and the *Preoccupation with relationships* scale assess the anxiety (over abandonment) dimension of the attachment style, whereas the *Discomfort with closeness* scale and the *Relationships as secondary* scale pertain primarily to the avoidance (of intimacy) dimension of the attachment style. *Discomfort with closeness* is a theme central to Hazan and Shaver's (1987) conceptualization of avoidant attachment. *Need for approval* reflects respondents' need for acceptance and confirmation from others, and characterizes Bartholomew and Horowitz's fearful and preoccupied groups (1991). *Preoccupation with relationships*, which involves an anxious and dependent approach to relationships, is a core feature of Hazan and Shaver's (1987)'s original conceptualization of anxious/ambivalent attachment. The *Relationships as secondary* scale is consistent with Bartholomew and Horowitz's concept of dismissing attachment (1991). Finally, *Confidence* (in self and others) reflects a secure attachment orientation.

The ASQ has been translated into Italian (Fossati et al., 2003); then, a consensus translation has been reached. This latter translation has been checked through back-translation by a native English-speaking professional translator. After three translations, the back version has been judged as adequately matching the original ASQ. The final translation has been sent to the author (J. Feeney) for her final approval. The Italian translation of the ASQ did not differ in any other respect from the original English version.

Data on construct and discriminant validity of the ASQ have been obtained by Fossati et al. (2003) in an Italian sample of 487 consecutively admitted psychiatric participants and an independent sample of 605 non-clinical parti-