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Platelet 18 kDa Translocator Protein density is reduced in depressed patients with adult separation anxiety

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Abstract

Rationale: Recent studies indicate that Adult Separation Anxiety Disorder (ASAD) may represent a discrete diagnostic entity worthy of attention. Adults with separation anxiety report extreme anxiety and fear about separations from major attachment figures (partner, children or parents). These symptoms affect individual's behavior, lead to severe impairment in social relationships and are not better accounted for by the presence of agoraphobia. In a previous study we found platelet expression reduction of the 18 kDa Translocator Protein (TSPO) (the new nomenclature for the peripheral-type benzodiazepine receptor) in patients with panic disorder who also fulfilled the diagnostic criteria for ASAD.
Objectives: To explore whether separation anxiety might be a factor differentiating TSPO expression in a sample of patients with major depression.
Methods: The equilibrium binding parameters of the specific TSPO ligand [^{3}H]PK 11195 were estimated on platelet membranes from 40 adult outpatients with DSM-IV diagnosis of MDD, with or without separation anxiety symptoms, and 20 healthy controls. Patients were assessed by SCID-I, HAM-D, the Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS-A) and the Adult Separation Anxiety Self-report Checklist (ASA-27).
Results: A significant reduction of platelet TSPO density mean value was found in depressed patients with associated ASAD symptoms, while no significant differences were found between depressed patients without ASAD and the control group. Individual TSPO density values were significantly and negatively correlated with both SCI-SAS-A and ASA-27 total scores, but not with HAM-D total score or HAM-D anxiety/somatization factor score.
Conclusions: The reduction of platelet TSPO density in our sample of patients with depression was specifically related to the presence of ASAD. These data suggest that TSPO expression evaluation is a useful biological marker of ASAD.

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1. Introduction

Separation anxiety (SA) has traditionally been defined as a childhood phenomenon. This disorder is conceptually rooted in both developmental research and attachment theory. Distress upon separation from one's attachment figure is the developmental norm during early childhood and is considered to be an evolutionarily adaptive mechanism designed to keep defenseless child in close proximity to his adult caregiver (Bowlby, 1973, 1982). Only when separation distress becomes prolonged, excessive, and developmentally inappropriate or impairing, is a psychiatric diagnosis typically made. The estimated prevalence of childhood separation anxiety disorder is 4% (APA, 2000). An adult form of this syndrome is contemplated by the DSM-IV. However, even when a distinctive constellation of SA symptoms is recognizable in the juvenile years and adulthood, a diagnosis is not usually made (Fagiolini et al., 1998). Manicavasagar et al. (1997) proposed that the core symptoms of SA – that is excessive and often disabling distress in the face of actual or perceived separation from major attachment figures – may indeed persist or arise throughout adulthood. Data from the National Comorbidity Survey – Revised indicate that Adult Separation Anxiety Disorder (ASAD) represents a discrete diagnostic entity worthy of clinical attention (Shear et al., 2006). Adults with ASAD report extreme anxiety about separation from major attachment figures (partner, children, or parents), fear that harm would befall those close to them and need to maintain proximity to them. These symptoms may affect the individual's behavior and lead to severe impairment in social relationships.

Data on relationships of SA symptoms with other adult anxiety or mood disorders are sparse in the literature. One hypothesis that persisted in the literature is that early SA is specifically linked to risk of panic disorder (PD) in adulthood (Klein, 1980). Indeed, with a few exceptions, the majority of earlier retrospective studies tended to support the SA-PD hypothesis (De Ruiter et and Van Ijzendoorn, 1992; Pine et al., 1998; Goodwin et al., 2001). Some other authors supported the hypothesis that early SA operates as a general vulnerability factor, increasing risk of anxiety and mood disorders in adulthood (Lipsitz et al., 1994). Lewinsohn et al. (1997), for example, in a large sample of young individuals, found that major depression (MDD) was significantly more likely to follow separation anxiety than PD.

Neurobiological knowledge about physiological changes related to separation from an attachment figure essentially derives from animal studies (Panksepp, 1998; Insel and Young, 2001; Zimmerberg et al., 2003; Neumann et al., 2005). However, literature data on human beings are limited (Vondra et al., 2001; Davis et al., 2003). Numerous studies have suggested that the 18 kDa Translocator Protein (TSPO) (the new nomenclature for the peripheral-type benzodiazepine receptor) (Papadopoulos et al., 2006a) is a promising biological marker as well as a diagnostic and therapeutic target of stress and anxiety. In fact, this mitochondrial protein, highly expressed in steroid synthesizing tissues, plays an important role in the regulation of cholesterol transport from the outer to the inner mitochondrial membrane, the rate-determining step in steroid biosynthesis (Lacapere et al., 2003). Upon TSPO activation by its specific ligands, neuroactive steroid formation has been reported to be increased (Papadopoulos et al., 2006b). These evidence suggested the TSPO involvement in the secretion of neurosteroids, whose levels are reported to be changed in several diseases and to be implicated in the pathogenic mechanisms of anxiety and mood disorders in humans (Heydari and Le Melledo, 2002; Strohle et al., 2002; Brambilla et al., 2003). In addition, TSPO density is changed in several psychopathological conditions: an up-regulation has been found to be associated with acute stress and down-regulation in chronic or repeated stress conditions (Gavish et al., 1999; Veenman and Gavish, 2006). A decreased TSPO density has been evidenced in blood cells (platelets or lymphocytes) of patients affected by different psychiatric disorders, mainly characterized by anxiety, such as generalized anxiety disorder (Weizman et al., 1987; Ferrarese et al., 1990; Rocca et al., 1991, 1998), generalized social phobia (Johnson et al., 1998), post-traumatic stress disorder (Gavish et al., 1996), panic disorder (Marazziti et al., 1994), chronic obsessive–compulsive disorder (Rocca et al., 2000) and also in suicidal patients (Soreni et al., 1999; Marazziti et al., 2005), as well as in healthy subjects with high trait anxiety levels (Nakamura et al., 2002). We have previously demonstrated that TSPO expression was significantly decreased in platelets of patients with panic disorder with severe separation anxiety symptoms but not in panic disorder patients without separation anxiety (Pini et al., 2005b). Major depressive disorder (MDD) has been reported to be not associated with TSPO density alterations (Weizman et al., 1995). The aim of the present study was to evaluate TSPO expression in platelets from patients with major depressive disorder (MDD) in relationship to the presence and severity of ASAD.

2. Materials and methods

2.1. Subjects and psychometric evaluation

A group of 40 adult outpatients (8 men and 32 women, mean age 44.0 ± 1.94 years, range 21–66) with a DSM-IV lifetime diagnosis of MDD, recruited and evaluated between May 2005 and April 2007 at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, of Pisa University, was included in the study. Twenty healthy drug-free subjects (controls) (6 men and 14 women, mean age 37 ± 3.28 years, range 23–62) with no family and personal history of psychiatric disorders or separation anxiety symptoms were also included in comparative analyses.

The control group was matched with patients for age, gender and season of blood sampling.

All patients were assessed with the SCID-I for principal diagnosis and for presence of Axis I comorbidity (First et al., 1996). Separation anxiety symptoms were evaluated in each subject by three instruments described in detail previously (Pini et al., 2005b), namely the Structured Clinical Interview for Separation Anxiety Symptoms—Childhood section (SCI-SAS-C) and —Adult section (SCI-SAS-A) (Cyranowski et al., 2002), the Separation Anxiety Symptoms Inventory (SASI) (Silove and Manicavasagar, 1993) and the Adult Separation Anxiety Questionnaire (ASA-27) (Manicavasagar et al., 2003). Childhood separation anxiety symptoms were retrospectively evaluated. The Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) was also administered to evaluate severity of depression. The anxiety component of depression was evaluated by using the HAM-D anxiety/somatization factor score as described by Fava et al. (2004). Rates of comorbid anxiety disorders, as evaluated by the SCID-I, were 42.5% (n=17) for panic disorder, 27.5% (n=11) for simple phobia, 10% (n=4) for social phobia and 5% (n=2) for obsessive–compulsive disorder.