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Behavioural effects of rapid intravenous administration of meta-chlorophenylpiperazine (m-CPP) in patients with generalized social anxiety disorder, panic disorder and healthy controls

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Abstract Findings from epidemiological, pharmacotherapeutical, genetic and neurobiological studies suggest a possible overlap in the neurobiology of generalized social anxiety disorder (gSAD) and panic disorder (PD). Previously we have found a rapid intravenous m-CPP challenge of 0.1 mg/kg to be highly sensitive and selective in the provocation of panic attacks in patients with PD. We therefore directly compared the behavioural, neuroendocrine and physiological effects of this rapid m-CPP challenge in a small sample of patients with gSAD, patients with PD and matched healthy controls. Panic attacks were significantly more provoked in patients with PD (85%), but not in patients with gSAD (14%) as compared to healthy controls (0%). Effects on the other behavioural parameters, but not on the neuroendocrine and physiological parameters, were significantly greater in patients with PD compared to patients with gSAD and controls. Our preliminary data do not support a shared neurobiology of gSAD and PD.

1. Introduction

Generalized social anxiety disorder (gSAD) and panic disorder (PD) are among the most prevalent anxiety disorders, with reported lifetime prevalences in Europe of 2.4% for SAD and of 2.1% for PD (Alonso et al., 2004a). In the United States lifetime prevalences of 3.4% for PD and 13.3% for SAD were found (Sheikh et al., 2002; Magee et al., 1996). PD and gSAD may cause severe social, occupational and academic impairment and typically have a chronic course. Although the two disorders clearly have a different core phenomenology, with spontaneous panic attacks occurring in PD and fear of scrutiny by others in gSAD, data from epidemiological, pharmacotherapeutical, genetic as well as a variety of neurobiological studies suggest an overlap in the neurobiology of gSAD and PD.

In epidemiological studies gSAD and PD are usually found to be highly comorbid conditions. Thus, in the European Study of the epidemiology of mental disorders (ESEMeD) the 12-month

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pair wise association between SAD and PD expressed in odd ratio's was 11.6 (Alonso et al., 2004b). Comparable to these findings in adult populations, the results of a recent large study in pre-adolescents indicated that, in a general population sample, it may not be useful to discern children with different types of anxiety symptoms (Ferdinand et al., 2006).

Pharmacotherapeutical studies have shown the efficacy of the selective serotonin reuptake inhibitors (SSRI's) in gSAD and PD, implicating the involvement of the serotonergic system in both disorders. However, tricyclic antidepressants and alprazolam have been found to be less effective in gSAD than in PD (Blanco et al., 2003; Kasper and Resinger, 2001; Zohar and Westenberg, 2000). At large, genetic studies seem to point at an anxiety diathesis model, i.e. a genetic predisposition to develop anxiety related symptoms and anxiety disorders. There seem to be genes that increase the risk only for specific disorders, as well as genes that increase the risk for anxiety disorders in general (Villafuerte and Burmeister, 2003; Hettema et al., 2005). Neuroimaging studies have shown the involvement of the same fear-circuitry in PD and in gSAD, but some differences have been found, notably in the involvement of elements of the dopaminergic system (Kent and Rauch, 2003; Charney, 2003).

A large number of studies on the neurobiology of gSAD and PD has employed challenge paradigms with anxiogenic or panicogenic pharmacological agents, often resulting in more or less comparable behavioural effects in patients with PD and patients with gSAD. However, only a small number of these studies directly compared the effects of the panicogenic challenge in patients with PD, patients with gSAD and matched healthy controls (Gorman et al., 1990; Papp et al., 1993; Caldirola et al., 1997; McCann et al., 1997; Tancer et al., 1994). We studied the effects of the rapid intravenous administration of 0.1 mg/kg meta-chlorophenylpiperazine (m-CPP), a (partial) 5-HT 2c receptor agonist that also possesses moderate to low affinity for other 5-HT receptors, as well as for (alpha2) adrenergic and dopamine receptors. We found this rapid intravenous m-CPP challenge to be highly sensitive and selective in the provocation of panic attacks in patients with PD as compared to healthy controls (panic attacks were provoked in 90% of the controls and in 0% of the healthy controls) (Van der Wee et al., 2004). We therefore decided to further elucidate the putative shared neurobiology of gSAD and PD by directly comparing the behavioural, neuroendocrine and physiological effects of the rapid intravenous administration of 0.1 mg/kg m-CPP in patients with gSAD, patients with PD, and matched healthy controls.

2. Experimental procedures

2.1. Subjects

Seven patients (five males, two females) with gSAD, seven patients with PD with or without agoraphobia and seven healthy controls participated in this study. Subjects were pairwise matched for sex, and group-wise on age. The diagnosis was made according to DSM-IV criteria, no axis I and no major axis II co-morbidity was allowed and the diagnosis was confirmed by the Mini International Neuropsychiatric Interview Plus 5.0.0 (Sheehan et al., 1998; Dutch version: Van Vliet and De Beurs, in press). In addition, no life time comorbidity between PD and gSAD was allowed. Subjects had no clinically significant medical disorders, were drug free for minimal 2 weeks (60 days for fluoxetine, 6 months for corticosteroids), had not donated blood during the 60 days preceding the test day, female subjects were not pregnant or breast-feeding, and all subjects had normal physical and laboratory examinations. There were no subjects with a history or suspicion of substance abuse. Subjects using drugs of abuse or more than 6 cups of coffee, 15 cigarettes or 3 units of alcohol a day, were excluded. The study was performed in the outpatient clinic of the University Medical Center Utrecht, the Netherlands, and was approved by the Medical Ethical Committee of the University Medical Center Utrecht. All subjects gave written informed consent prior to inclusion in the study.

2.2. Procedures

We used the same single blind, comparative design, as in our previous study (Van der Wee et al., 2004). Subjects were told that they would receive either m-CPP or a solution mimicking some of the side-effects of m-CPP (i.e. hot and cold flushes and dizziness). In reality all subjects received m-CPP. Subjects took a light breakfast at least one hour before the test. Coffee, smoking and alcoholic beverages were not allowed from 9 p.m. on the evening before. Immediately after baseline assessments an indwelling intravenous catheter was placed in a forearm vein in each arm at 9.00 a.m. At 10.00 a.m. m-CPP (0.1 mg/kg diluted in 20 ml of normal saline) was administered in 90 s by means of an automatic pump (Becton Dickinson). Behavioural, physiological and neuroendocrine responses, as well as m-CPP plasma levels were measured immediately before infusion and at 30-minutes intervals until 150 min after infusion.

2.3. Behavioural assessments

Behavioural responses were measured prior to the measurement of physiological and neuroendocrine responses. Behavioural responses were assessed by using a Visual Analogue Scale (VAS) for anxiety and the Panic Symptom Scale (PSS) (Bradwejn et al., 1992; Van Megen et al., 1994, 1996). The VAS for anxiety was used to evaluate the change in anxiety, with a score range from 0 = not at all to 100 = most ever. The PSS is a self-rating instrument derived from DSM-III-R criteria for a panic attack. Both the symptom severity and the fear of the symptom are rated on a 5-point scale (0 = not at all to 4 = severe).

After the challenge the occurrence of panic attacks (the main outcome measure) was assessed. A panic attack had to fulfil the following criteria: subjects had to experience a feeling of panic, had to have an increase of at least four of the 13 DSM-IV symptoms of a panic attack, as extracted from the PSS, combined with a score of two or more on the item 'Apprehension' of these four symptoms. Subjects had to report that the panic attack was similar to their spontaneous ones when applicable.

2.4. Vital signs

Temperature (orally measured), systolic and diastolic blood pressure (supine after 5 min rest; standing after 1 min standing), and heart rate (supine after 5 min rest; standing after 1 min standing) were recorded. Blood pressure and heart