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Acute panicogenic, anxiogenic and dissociative effects of carbon dioxide inhalation in patients with post-traumatic stress disorder (PTSD)

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ABSTRACT

Background: Increased anxiety and panic to inhalation of carbon dioxide (CO_2) has been described in patients with anxiety disorders, especially panic disorder, compared to healthy subjects. Post-traumatic stress disorder (PTSD) has been hypothesised to resemble panic disorder and is currently classified as an anxiety disorder in DSM-IV. However, there are only very few data available about the sensitivity of patients with PTSD to CO_2.
Methods: In 10 patients with PTSD, 10 sex- and age-matched healthy subjects and 8 patients with panic disorder we assessed anxiety, panic, dissociative and PTSD symptoms before and after a single vital capacity inhalation of 35% CO_2.
Results: Patients with PTSD showed an increased anxiety, panic and dissociative reaction to the inhalation of 35% CO_2 compared to healthy participants. PTSD subjects' responses were indistinguishable from those of panic patients. Additionally, PTSD-typical symptoms like post-traumatic flashbacks were provoked in patients with PTSD after the inhalation of CO_2.
Conclusions: In our sample, PTSD was associated with an increased CO_2 reactivity, pointing to an increased susceptibility of PTSD patients to CO_2 challenge.

1. Introduction

Autonomic arousal and arousability, clinically characterised by symptoms such as shortness of breath, rapid heartbeat, and trembling, are shared features of the DSM-IV anxiety disorder constructs panic disorder (PD) and post-traumatic stress disorder (PTSD) (Brown and McNiff, 2009). In addition to salient similarities in the phenomenology of panic attacks and re-experiencing (intrusive) symptoms of PTSD (Mellman and Davis, 1985), some panic provoking agents, such as intravenous sodium lactate, yohimbine, meta-chlorophenylpiperazine (mCPP) and cholecystokinin-tetrapeptide (CCK-4) have been reported to elicit not only panic attacks, but also post-traumatic flashbacks or other PTSD symptoms in patients with PTSD (Jensen et al., 1997; Kellner et al., 1998, 2000; Rainey et al., 1987; Southwick et al., 1993, 1997). Only the putative panicogen flumazenil did not induce panic anxiety or PTSD symptoms in these patients (Coupland et al., 1997; Randall et al., 1995).

Another useful paradigm to study panic anxiety is inhalation of carbon dioxide (CO_2) (Rassovsky and Kushner, 2003). Inhalation of a single deep breath of 35% CO_2 has proved to be a reliable panicogenic challenge model in patients with PD (Verburg et al., 1998a). Healthy subjects who underwent a double inhalation of different dosages of CO_2 reported a negative affect with somatic and cognitive symptoms similar to a panic attack correlating to the amount of CO_2 administered (Griez et al., 2007). Individual response to CO_2 inhalation has been investigated as a putative intermediate phenotype of susceptibility to panic disorder in the general population (Ogliari et al., 2010).

One primary theory of the mechanisms of the CO_2 responsitivity is that of Klein (1993), who suggested that panic disorder patients have increased CO_2 sensitivity of their central chemoreceptors, and thus are more likely to experience a 'suffocation false alarm' that in turn leads to panic. In preclinical investigations an acid-sensing ion channel in the amygdala has been identified as an important chemosensor for hypercapnia eliciting fear responses (Ziemann et al., 2009). Further research suggests that the administration of CO_2 leads to non-specific activation of a complex brain fear-network including the amygdala, the hippocampus and the medial prefrontal cortex (Gorman et al., 2000, 2001). Potentially the noradrenergic system, particularly the locus coeruleus, plays an important role in this network-activation (Bailey et al., 2003). In a recent review Esquivel et al. (2010) postulated that inhalation of

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CO_2 leads to disturbances in cerebral pH homeostasis and provokes negative emotions ranging from breathlessness to panic. These non-specific interoceptive disturbances might be subsequently misinterpreted as catastrophic ("danger of impending suffocation") by patients with anxiety disorders and lead to immediate urgency to breathe (Rassovsky et al., 2006; Colasanti et al., 2008).

For patients suffering from PTSD, only one investigation has so far characterised the effect of CO_2 inhalation: Talesnik et al. (2007) reported a lack of sensitivity to a single vital capacity inhalation of 35% CO_2 measuring panic anxiety and post-traumatic symptoms in patients with PTSD. Findings about possible alterations of CO_2 partial pressure have been contradictory in PTSD patients: End-tidal CO_2 partial pressure at rest was found to be significantly lower compared to healthy controls by Rosen et al. (1994), while Blechert et al. (2007) did not detect respective differences between patients with PTSD compared to healthy controls and patients with PD.

We studied the effects of CO_2 (35%) on panic anxiety and PTSD symptoms in subjects with PTSD, healthy matched controls and, to be sure of the assay sensitivity, panic patients as an additional positive control group. We hypothesised increased susceptibility concerning provocation of panic, anxiety and dissociative symptoms in PTSD patients versus healthy control subjects in this paradigm and expected provocation of post-traumatic flashbacks and other PTSD symptoms.

2. Methods and materials

2.1. Participants

Patients with PTSD or PD admitted to the Department of Psychiatry and Psychotherapy were invited to participate. 10 adult patients with chronic PTSD (7 women, 3 men, mean age 32.3 ± 7.7 years) and 10 healthy sex- and age-matched controls (mean age 32.3 ± 8.5 years) were included in the study. Furthermore, 8 adult patients with PD (1 woman, 7 men, mean age 35.0 ± 5.4 years) were enrolled as an additional positive control group with known increased susceptibility to CO_2 challenge. All patients were examined during a preparation period before an exposure therapy.

All subjects were assessed with the Structured Clinical Interview of DSM-IV (SCID, German version; Wittchen et al., 1997). Exclusion criteria were a psychotic, organic or substance related disorder for the patient groups, comorbidity with panic disorder for the PTSD patients, comorbidity with PTSD for the panic patients and any psychiatric disorder for healthy controls. The latter group also had to avoid of a psychiatric family history and a personal history of a singular panic attack. Additional exclusion criteria were substantial respiratory and cardiocirculatory disorders including arterial hypertension, personal or family history of cerebral aneurysm, pregnancy, or epilepsy. All patients had to be drug-naïve or drug free for at least 2 weeks. All participants had undergone a thorough medical examination including urinary drug screens.

Trauma history was assessed by clinical exploration and the Post-traumatic Diagnostic Scale (PDS) (Foa et al., 1997). The PTSD qualifying events in the group of PTSD patients were rapes/sexual abuse ($n = 6$), witnessing suicide ($n = 1$), assaults ($n = 1$), accidents ($n = 1$) and combat ($n = 1$). We also assessed panic and anxiety symptoms with the Panic and Agoraphobia Scale (PAS) (Bandelow et al., 1995).

The protocol was approved by the Ethics Committee of the Medical Board Hamburg and each participant gave written informed consent.

2.2. Carbon dioxide challenge

We used a mixture of 35% CO_2 and 65% oxygen in our study. First, we measured vital capacity of the participants by a respirometer (JS Medizintechnik, Germany). After that we instructed the participants to exhale as much air as possible and then to take a very deep breath of the gas mixture through a face mask and hold their breath for 3 s and exhale. Each subject inhaled a single inhalation of at least 80% of vital capacity controlled by a volumeter.

The primary outcome measure was the increase of Acute Panic Inventory (API) (Dillon et al., 1987) ratings from just before the inhalation to after the inhalation. As secondary outcome parameters we measured anxiety and panic symptoms by a 100 mm Visual Analogue Scale for anxiety (VAS "anxiety") and the Panic Symptoms Scale (PSS), which consisted of the 13 DSM-IV symptoms of a panic attack. Dissociative symptoms were rated by the dissociative subscale of the Acute Dissociative Inventory (ADI) (Leonard et al., 1999). Additionally, we assessed PTSD symptoms by the Flashback questionnaire (Kellner et al., 2000) and the PTSD Symptom Scale before and after the inhalation (Southwick et al., 1993).

2.3. Statistical analyses

Differences in age and sex between the three groups were tested using oneway analysis of variance and a chi-square test (Fisher's exact test), respectively.

Analyses of variance were used to test about significance the group effect a) on the changes (differences) of API-scores and b) on the changes of ADI-, VAS- and PSS-scores before and after inhalation of CO_2. Whenever significant group effects were found, univariate *F*-tests followed to identify those variables which contribute significantly to the group effects. For these variables post-hoc contrast tests were performed to locate pairs of groups with significant differences in their means.

A *t*-test of paired samples test was applied to compare the pre- and post-CO_2 ratings of PTSD Symptom Scale in the PTSD patients.

As nominal level of significance, $a = 0.05$ was accepted. All post-hoc tests (univariate *F*-Tests and contrast tests) were performed at a reduced level of significance (Bonferroni procedure) to keep the type I error less or equal to 0.05. All values are given as mean ± SEM.

3. Results

3.1. Study sample

Ten patients with PTSD, ten matched control subjects and eight patients with PD were studied. Age was not significantly different among the three study groups ($F(2,25) = 0.39$, sig of $F = 0.682$, effect size = 0.17). Concerning sex, significant differences among groups emerged (Fisher's exact test: $p = 0.031$), which were localised only between the panic patients and the other two groups (more male participants in the group of patients with PD; $p < 0.05$), but not between PTSD patients and control subjects.

In the group of PTSD patients severity of PTSD according to PDS ratings was 27.8 (±10.1), which is medium severity. In this group six patients (four female and two male) had a comorbid major depression, two female patients had a comorbid bulimia nervosa and one female patient had a comorbid obsessive-compulsive disorder according to SCID-I interview. Two of our patients had a history of self-harming.

Panic patients had a PAS score of 25 (±10.1), which is medium severity. In this group one male participant had a comorbid major depression according to SCID-I interview.

3.2. Increase of Acute Panic Inventory (API)

Inhalation of CO_2 resulted in increased ratings of panic anxiety on the API, our main outcome parameter, in all groups (Fig. 1). Statistical analysis revealed a significant group effect on the increments (differences from post- to pre-scores) ($F(2,25) = 6.97$, sig of $F = 0.004$, effect