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Physiological and affective reactivity to a 35% CO_2 inhalation challenge in individuals differing in the 5-HTTLPR genotype and trait neuroticism

Ellen Verschoor, C. Rob Markus*

Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands

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Abstract

The inhalation of 35% carbon dioxide (CO_2) results in an acute stress response in healthy individuals and may accordingly provide a good paradigm to examine potential vulnerability factors for stress reactivity and stress-related psychopathology. It has been proposed that CO_2 reactivity is moderated by genetic (5-HTTLPR) and personality (neuroticism) factors, yet no experimental study has investigated their effects on CO_2 reactivity simultaneously. The current study examined the singular and interactive effects of the 5-HTTLPR genotype and neuroticism in predicting the affective and physiological response to a 35% CO_2 challenge in a healthy sample of male and female students. From a large group of 771 students, 48 carriers of the low/low expressing allele (S/S, S/Lg, Lg/Lg) and 48 carriers of the high/high expressing allele (La/La) with the lowest and the highest neuroticism scores (77 females, 19 males; mean age ± SD: 20.6 ± 2 years) were selected and underwent a 35% CO_2 inhalation. Visual analogue scales for anxiety and discomfort and the Panic Symptom List were used to assess affective symptomatology, while salivary samples and heart rate were assessed to establish the physiological response. A typical pattern of responses to CO_2 was observed, characterised by increases in anxiogenic symptoms and physical panic symptomatology and a reduction in heart rate; however, no effect on salivary cortisol concentration was observed. Additionally, the CO_2 reactivity did not differ between groups divided by the 5-HTTLPR genotype or neuroticism. Findings of the current study do not support a role for singular or interactive effects of the 5-HTTLPR genotype and trait neuroticism on affective and physiological reactivity to a 35% CO_2 inhalation procedure.

1. Introduction

Previous research has shown that the hypercapnia caused by inhalation of 35% carbon dioxide (CO_2) induces anxiogenic,

* Corresponding author. Tel.: +31 43 3882474; fax: +31 43 3884196.
E-mail address: r.markus@maastrichtuniversity.nl (C.R. Markus).

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neuroendocrine and autonomic responses (Kaye et al., 2004; Van Duinen et al., 2007; Wetherell et al., 2006). Although individuals with panic disorders are most susceptible, also healthy individuals experience an affective and a physiological stress response after a 35% CO_2 inhalation procedure (Argyropoulos et al., 2002; Griez et al., 2007; Van Duinen et al., 2005). Consequently, it is suggested that the CO_2 paradigm is useful to induce acute stress in a standardized laboratory setting (Argyropoulos et al., 2002; Kaye et al., 2004; Wetherell et al., 2006). In addition, since maladaptive stress responses are involved in a wide range of psychopathological processes (Bale, 2006), the CO_2 paradigm may be used to unravel individual differences in vulnerability for stress and stress-related disorders.

Abundant evidence suggests that CO_2 reactivity might be partially driven by serotonin (5-hydroxytryptamine, 5-HT). Increasing brain 5-HT, via its precursor L-tryptophan or via serotonergic agonists, reduces the anxiogenic effects of CO_2 (Mortimore and Anderson, 2000; Schruers and Griez, 2004; Schruers et al., 2002), whereas diminishing 5-HT via tryptophan depletion or 5-HT antagonists increases CO_2 responsiveness (Ben-Zion et al., 1999; Kent et al., 1996; Klaassen et al., 1998; Meiri et al., 2001; Miller et al., 2000; Schruers et al., 2000).

Interestingly, 5-HT function is regulated by the gene SLC6A4 that controls the 5-HT transporter (5-HTT) (Heils et al., 1996; Lesch et al., 1996). The promoter region of this gene reveals a functional variable repeat sequence polymorphism (5-HTTLPR) including a low expressing or short (S) and a high expressing or long (L) allelic variant; of which the former is less active and causing lower 5-HTT binding and mRNA expression (Hariri and Holmes, 2006; Heils et al., 1996; Lesch et al., 1996). Recently, the presence of an A>G single nucleotide polymorphism has been identified in the high (L) expressing allele, rendering an Lg variant (as opposed to La) that is functionally equivalent to the low expressing (S) allele.

In a prominent study by Caspi et al. (2003) S-allele carriers appeared to be more vulnerable to the depressogenic effects of stressful life events than subjects carrying two copies of the L-allele. Comparable findings have been replicated by other groups (for a review, see Uher and McGuffin, 2008; 2010) and — contrary to the results of two smaller earlier meta-analyses (Munafo et al., 2009; Risch et al., 2009) — receive strong support from a recent elaborated meta-analysis (Karg et al., 2011). In addition, abundant imaging (see Munafo et al., 2008) and acute laboratory stress studies (Alexander, et al., 2009; Dougherty, et al., 2010; Gotlib, et al., 2008; Mueller et al., 2010; Way and Taylor, 2010; Markus and De Raedt, 2011) reveal that carrying one or two copies of the low expressing S-allele increasingly promotes susceptibility to psychosocial stressors (see Uher and McGuffin, 2008, 2010).

Based on the role of the 5-HTTLPR genotype in stress reactivity, it is tempting to explore whether this genotype will also mediate CO_2 reactivity. From three studies that have evaluated this relationship (Perna et al., 2004; Schmidt et al., 2000; Schruers et al., 2011) two studies (Schmidt et al., 2000; Schruers et al., 2011) surprisingly showed increased affective CO_2 responses in homozygous L-allele carriers. Yet, these results could not be replicated in patients with panic disorder (Perna et al., 2004).

Although biological factors inevitably contribute to the adverse reactions to stress or CO_2 challenge, psychological variables serve at least an equally important role (Zvolensky and Eifert, 2001). With respect to CO_2 sensitivity, previous research has shown that high scores on trait anxiety, anxiety sensitivity and suffocation fear promote CO_2 responsiveness (for review, see Zvolensky and Eifert, 2001). Moreover, one study examined a 5-HTTLPR by anxiety interaction on CO_2 reactivity (Schmidt et al., 2000) and revealed that high anxious L-allele carriers showed the highest CO_2 reactivity.

Another cognitive-psychological parameter implicated in stress and that hence might also play a role in CO_2 reactivity is the personality trait neuroticism. Trait neuroticism refers to individual differences in emotional stability, negative emotional responses to threat, frustration, or loss and is operationally defined by items referring to irritability, sadness, worry and self-consciousness (Lahey, 2009). Individuals with high trait neuroticism are more likely to attribute events as stressful (Kendler et al., 2003), possess less (believe in) adaptive coping strategies (Shoji et al., 2009) and are vulnerable to develop stress-related pathology (for a meta-analysis, see Malouff et al., 2005). To the best of the authors' knowledge, so far one study examined the effect of neuroticism on CO_2 reactivity; reporting a positive association on panic responses (Coryell et al., 2006).

The current study examined the interaction between 5-HTTLPR and trait neuroticism on CO_2 reactivity in healthy male and female students. Homozygous low-expressing allele carriers (S/S, S/L_G and L_G/L_G, expressed as low/low) and homozygous high-expressing allele carriers (L_A/L_A, expressed as high/high) (N=96) with the lowest and the highest neuroticism scores were selected from 5-HTTLPR genotyped undergraduate students (N=771). Affective symptomatology, salivary cortisol concentration and heart rate were assessed before and after a double 35% CO_2 inhalation. It was hypothesized that 5HTTLPR influences CO_2 reactivity conditional to trait neuroticism.

2. Experimental procedures

2.1. Participants

As part of a large Gene×Stress×Neuroticism research project, undergraduate students (N=1300) at Maastricht University received a questionnaire screening package concerning general information (health, personal or family history of medical or psychiatric complaints, smoking and drinking habits, caffeine consumption, weight and height, use of psychoactive drugs) and the Beck Depression Inventory (BDI; Beck et al., 1961) to verify the absence of depressive symptomatology. Participants were excluded for further evaluation if they reported chronic or current physical or psychiatric illness; family history of psychiatric illness; the presence of hypertension (diastolic >100 mm Hg; systolic >170 mm Hg), cerebral aneurysma, epilepsy, medication use; a Body-mass Index (BMI) below or above 20–24 kg/m^2; smoking; excessive use of alcohol (>2 units a day), coffee (>10 units a day) or other drugs; non-Caucasian race and pregnancy. Following this first selection, 793 participants were invited to visit the laboratory for a buccal sample extraction session for genotyping and to complete individual assessment for neuroticism scores (see Physiological measures). Twenty-two participants did not respond to the invitation to visit the laboratory and, hence, data on the 5-HTTLPR genotype and neuroticism were available for 771 participants (low/low or S′/S′, n=158, high/low