Psychiatry Research 178 (2010) 342–347

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Associations between personality traits and CCK-4-induced panic attacks in healthy volunteers

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ARTICLE INFO

Article history:
Received 24 September 2009
Received in revised form 30 March 2010
Accepted 1 April 2010

Keywords:
Cholecystokinin
Anxiety

ABSTRACT

In this study we examined how personality disposition may affect the response to cholecystokinin tetrapeptide (CCK-4; 50 μg) challenge in healthy volunteers ($n=105$). Personality traits were assessed with the Swedish universities Scales of Personality (SSP). Statistical methods employed were correlation analysis and logistic regression. The results showed that the occurrence of CCK-4-induced panic attacks was best predicted by baseline diastolic blood pressure, preceding anxiety and SSP-defined traits of lack of assertiveness, detachment, embitterment and verbal aggression. Significant interactions were noted between the abovementioned variables, modifying their individual effects. For different subsets of CCK-4-induced symptoms, the traits of physical aggression, irritability, somatic anxiety and stress susceptibility also appeared related to panic manifestations. These findings suggest that some personality traits and their interactions may influence vulnerability to CCK-4-induced panic attacks in healthy volunteers.

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1. Introduction

In the past decades several neurobiological and psychological factors have been identified to play a crucial role in the pathophysiology of panic disorder (PD). As the experimental induction of panic attacks offers a unique opportunity to study the core symptoms of PD under controlled conditions, several panic challenge procedures have been established to investigate the mechanisms of panic attacks and anxiolytic treatments. Panic induction with cholecystokinin-tetrapeptide (CCK-4) or pentagastrin (CCK-5) has been established as a valid experimental model of human panic attacks. CCK-4 and CCK-5 are synthetic analogues of the endogenous neuropeptide cholecystokinin (CCK) acting as agonists of the central subtype of CCK receptors to induce panic attacks in patients with PD and, to a lesser extent, in healthy subjects (Bradwejn et al., 1991; Abelson and Nesse, 1994). The CCK-induced panic symptoms resemble spontaneous panic attacks in PD patients (Bradwejn et al., 1991; Abelson and Nesse, 1994), suggesting the suitability of such experimental challenge setting to clinical investigation of panic phenomena. The mechanisms underlying panic induction by CCK-4 are not yet fully understood. Although previous studies have accounted for CCK-4-induced panic response through mainly biological mechanisms, the somewhat contradictory data suggest that cognitive appraisal, fear of anxiety sensations, some personality traits and baseline anxiety may have at least some role (Koszycki et al., 1993, 1996; Flint et al., 1998; Aluoja et al., 1997). Koszycki et al. (1996) found that in patients with PD ($n=29$), anxiety sensitivity, a trait characterized by the propensity to appraise symptoms of anxiety as threatening, correlated significantly with cognitive, but not with somatic or affective, response to CCK-4. Radu et al. (2003) demonstrated that in healthy volunteers ($n=20$), the Anxiety Sensitivity Index scores correlated with ratings of anxiety and discomfort following the administration of pentagastrin. However, several studies have observed that anxiety sensitivity did not predict panic response to CCK-4 in healthy subjects (Koszycki et al., 1993 ($n=36$); Flint et al., 1998 ($n=80$)). Furthermore, Van Megen et al. (1994) found no association between the fear of anxiety-related symptoms and response to pentagastrin in patients with PD ($n=30$). The associations between baseline state or trait anxiety and response to CCK-4 also vary from study to study. While Radu et al. (2003) showed that in healthy volunteers, baseline state anxiety correlated with anxiety/discomfort reaction after the administration of pentagastrin, Aluoja et al. (1997) in their study on healthy volunteers ($n=14$) found that state/trait anxiety predicted the reaction to placebo, but not to CCK-4. Also, Eser et al. (2008), studying the impact of state and trait anxiety on CCK-4-induced panic in healthy volunteers ($n=33$), found no significant differences between the groups of panickers and non-panickers.

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doi:10.1016/j.psychres.2010.04.003

Among basic personality traits, introversion and neuroticism may have some relationships with CCK-4-induced panic. Koszycki et al. (1996) found significant correlations between the scores of Minnesota Multiphasic Personality Inventory (MMPI) Social Introversion scale and somatic, cognitive, and affective response to CCK-4 in patients with PD. Koszycki and Bradwejn (1997) also found an inverse relationship between the scores of extraversion on the Eysenck Personality Questionnaire and baseline nervousness in healthy males ($n=40$). Extraversion scores correlated positively with the onset of CCK-4-induced symptoms and some physiological indices. The same study showed that neuroticism correlated positively with pre-challenge self-rated nervousness, the number of CCK-4-induced symptoms, and post-challenge self-rated anxiety, nervousness and fearfulness. Predisposing influence of negative affect on panic reaction in response to a biological challenge was further supported by Radu et al. (2003), showing that Karolinska Scales of Personality subscales of Muscular Tension, Indirect Aggression, Verbal Aggression and Suspicion were associated with the anxiety reaction to pentagastrin. This brings attention to the possible role of aggression-related traits in panic reaction to CCK-4. However, the predictive value of personality traits in CCK-4 challenge studies has been equivocal. Eser et al. (2007) studying healthy males ($n=85$) found no correlation between CCK-4-induced panic symptom severity and any of the revised Minnesota Multiphasic Personality Inventory (MMPI-2) subscales. Furthermore, the MMPI-2 clinical scales did not correlate with panic status according to either panic criterion posed by the authors. These discrepancies warrant further exploration of the role of personality in laboratory panic, especially in larger samples, which could yield more reliable results compared with the relatively small samples of previous studies.

We aimed to test the hypothesis that susceptibility to CCK-4-induced panic attacks in healthy subjects is influenced by anxiety-related personality traits. Based on the findings outlined above, we hypothesized that (a) higher pre-challenge anxiety will be associated with a stronger panic reaction to CCK-4 challenge; (b) some SSP anxiety-related traits will predict the emergence and magnitude of the panic reaction—specifically, somatic trait anxiety will predict somatic symptoms and psychic trait anxiety will predict cognitive symptoms of panic; and (c) SSP detachment and trait aggression scores will predict CCK-4-induced panic reaction.

2. Methods

2.1. Subjects

A total of 105 healthy volunteers (mean age 22.4, range 18–49, 55% females) were recruited by flyer advertisements. All subjects gave written informed consent after learning about the study aims and procedures. The study protocol and informed consent form were approved by the Human Studies Ethics Committee of the University of Tartu, Estonia. The inclusion criteria were age between 18 and 50 years, no personal or family (first degree relatives) psychiatric history, negative urine drug screen and good physical health. Pregnancy was excluded with a urine pregnancy test.

2.2. Assessments

The diagnostic assessment was done using the Estonian translation of the Mini International Neuropsychiatric Interview (M.I.N.I. 5.0.0; Sheehan et al., 1998). Baseline anxiety and depression were measured by the clinician-rated Hamilton Anxiety Scale (HAS; Hamilton, 1969) and two subscales of the self-rated Emotional State Questionnaire (EST-Q; Aluoja et al., 1999) measuring the symptoms of depression and anxiety during past four weeks. Personality traits were assessed with the Swedish universities Scales of Personality (SSP; Gustavsson et al., 2000; Aluoja et al., 2009), a self-rated questionnaire based on the Karolinska Scales of Personality (Schalling, 1978). The SSP comprises 91 items grouped into 13 scales: Somatic Trait Anxiety (STA), Psychic Trait Anxiety (PsTA), Stress Susceptibility (SS), Lack of Assertiveness (LA), Impulsiveness (I), Adventure Seeking (AS), Detachment (D), Social Desirability (SD), Embitterment (E), Trait Irritability (TI), Mistrust (M), Verbal Trait Aggression (VTA), and Physical Trait Aggression (PhTA). Each scale is formed by 7 items rated on a scale of 1 (does not apply at all) to 4 (applies completely). Factor analysis suggested that SSP scales measure three broad constructs: neuroticism, extraversion and aggressiveness (Gustavsson et al., 2000). The Estonian translation of SSP has previously been validated showing a factor structure similar to the original version (Aluoja et al., 2009). The subjective effects of CCK-4 challenge were assessed by Visual Analogue Scales (VAS), based on scales of Bond et al. (1974), consisting of 100 mm lines for the dimensions of anxiety (VAS-A) and discomfort (VAS-D). CCK-4-induced symptoms were rated on the Panic Symptom Scale (PSS; Bradwejn et al., 1991) assessing the intensity of 18 symptoms derived from the DSM-III-R/IV criteria for panic attack from 0 (not present) to 4 (extremely severe). The main outcome variable was occurrence of a panic attack. The *a priori* criteria to define the panic attack were a sudden onset of at least 4 PSS symptoms of at least moderate intensity (score ≥ 2) and anxiety/apprehension/fear PSS item scored as at least 3 (severe or extreme). Other measures derived from the PSS were the number of symptoms (number of items scored ≥ 1), sum intensity score (the sum of all individual item ratings), and subscale scores for somatic and cognitive symptoms. Arterial blood pressure (BP) and heart rate (HR) were measured with an automatic sphygmomanometer (Dinamap Pro 100, Criticon, Tampa, FL, USA). Maximum changes in the studied parameters were calculated by subtracting baseline scores from the highest values obtained within 90 s after injection.

2.3. Procedures

The subjects arrived at the research unit on the challenge day at about 10:00 am. Upon arrival, they completed the EST-Q and HAS. Then, an intravenous cannula was inserted into an antecubital vein and saline infusion was started to keep the cannula open. The subjects stayed in the same room resting. At 11 am, after the registration of baseline values of BP, HR and VAS-A, a bolus injection of 50 μg of CCK-4 (Clinalfa, Merck Biosciences AG, Switzerland) diluted in 2.5 ml of normal saline solution was given through the cannula (during ca 3 s). The subjects were asked to describe any symptoms they experienced after the injection. The BP, HR and VAS-A were registered every 30 s for 2 min, then at 5 and 15 min. After the CCK-4-induced symptoms had abated, the subjects were assessed on PSS and rated VAS-A and VAS-D for the peak symptoms. After completion of the last measurements the cannula was removed and the subject was allowed to leave when comfortable with an option of phone contact over the next 24 h.

2.4. Data analysis

For comparison of the groups with and without panic reaction we used *t*-tests for normally distributed data and Mann–Whitney *U* tests for the rest of the variables. Correlation analysis was done to investigate the relationships between the continuous or nearly continuous variables. A logistic model was developed to determine the variables possibly predicting the occurrence of panic attack. All possible main-effect models that did not contain interaction terms with up to 10 parameters (out of 23 possible) were created. After excluding the models with the parameters resulting in multicollinearity, three models with the least Akaike's information criterion (AIC) were chosen for detailed investigation. Adding quadratic terms did not decrease AIC. The interaction terms which improved AIC were added to the models. For easier interpretation of interactions, the models were fitted to standardised data. Finally, to find out if the model with better AIC was also significantly better by likelihood, the log-likelihood chi-squared tests were performed. Correlation analysis was conducted to examine how personality traits were associated with the number of panic symptoms, self-assessed discomfort and anxiety. In addition to investigating predictive values of personality traits, regression models were developed for the PSS total, somatic and cognitive scores, number of panic symptoms, and VAS-A and VAS-D by stepwise regression towards minimizing AIC. For PSS symptoms, Poisson regression was used; in other cases, response variables (or suitably transformed response variables) followed normal distribution and ordinary linear regression models were developed. The data were controlled for multiple testing where appropriate and power analyses were performed ad hoc. The *R* and Stata statistical software were used for the data analysis.

3. Results

Forty seven subjects (45%) met the study definition for a CCK-4-induced panic attack. Panic rate was not different between male and females. The comparison of mean values and predictor variables between panic and non-panic groups is presented in Table 1. Among all variables only age and the scores on Verbal Trait Aggression subscale were significantly different between the groups. After Holm–Bonferroni correction for multiple testing none of the comparisons retained significant difference. None of the pairwise comparison tests achieved 80% power (min 5%, max 62%). The sample sizes required to achieve 80% power with the observed effect sizes assuming similar panic attack rates are shown in Table 1.

The comparison of logistic regression models indicated that the best set (by AIC) of variables predicting the occurrence of PA included baseline diastolic blood pressure (RRD-0; lower values result in higher chance of PA), baseline anxiety (EST-Q-A; higher scores give higher chance of PA), SSP Lack of Assertiveness (LA; higher scores result in higher chance of PA), SSP Verbal Trait Aggression (VTA; higher scores

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