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Functional magnetic resonance imaging characterization of CCK-4-induced panic attack and subsequent anticipatory anxiety

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The main objective of this work was to study the functional markers of the clinical response to cholecystokinin tetrapeptide (CCK-4). Twelve healthy male subjects were challenged with CCK-4 and simultaneously underwent functional magnetic resonance imaging (fMRI) recording. Since anticipatory anxiety (AA) is an intrinsic part of panic disorder, a behavioral paradigm, using the threat of being administered a second injection of CCK-4, has been developed to investigate induced AA. The study was composed of three fMRI scans according to an open design. During first and second scan, subjects were injected with placebo and CCK-4, respectively. The third scan was the AA challenge. CCK-4 administration induced physiological and psychological symptoms of anxiety that met the criteria for a panic attack in 8 subjects, as well as cerebral activation in anxiety-related brain regions. Clinical and physiological response intensity was consistent with cerebral activity extent and robustness. fMRI proved more sensitive than clinical assessment in evidencing the effects of the AA challenge. The latter induced brain activation, different from that obtained on CCK-4 and during placebo injection, that was likely related to anxiety. The method applied in this study is suitable for the study of anxiety using fMRI.
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Keywords: Panic attack; CCK-4; Anticipatory anxiety; fMRI; Human models

Introduction

Panic disorder (PD) is an incapacitating condition with long-term negative consequences. Lifetime prevalence is approximately between 2.5 and 3.5% (Kasper and Resinger, 2001). PD is characterized by recurring panic attacks (PA), which include intense anxiety, somatic, sensory and cognitive symptoms (APA, 1994). Despite intensive preclinical and clinical research efforts, the understanding of PA and PD pathophysiology is still at an embryonic stage. The unpredictability and rapid onset/offset of panic symptoms make it difficult to investigate various symptoms and signs during spontaneous attacks and therefore to study PA in patients directly. However, PA can be induced experimentally using probes such as caffeine, fenfluramine, isoproterenol, procaine, sodium lactate, carbon dioxide, yohimbine, *m*-chlorophenyl-piperazine and cholecystokinin (CCK) tetrapeptide (CCK-4) (Price et al., 1995).

In the present study, we have chosen to use CCK-4 to induce attenuated panic-like symptoms based on the following reasons: (1) CCK-4 is found in high amounts in brain areas involved in emotional and cognitive processes, and it appears as the only pharmacological probe that fulfills the criteria for a neurotransmitter (for review, see Van Megen et al., 1996); (2) CCK-4 reliably reproduces somatic, sensorial and cognitive signs of PA in a dose-dependent manner both in panic patients and healthy subjects, but with a higher rate in the former (Bradwejn et al., 1991); (3) its use in humans was shown to be safe (e.g., short half-life, symptoms of short duration); (4) CCK-4-induced symptoms are reproducible (Depôt et al., 1999; Van Megen et al., 1997) and can be reversed by approved anxiolytic drugs such as benzodiazepines (de Montigny, 1989), imipramine (Bradwejn and Koszycki, 1994), fluvoxamine (Van Megen et al., 1997) and citalopram (Shlik et al., 1997). All these data suggest that the CCK-4 model fulfills the criteria for an ideal model of anxiety (Guttmacher et al., 1983).

Only two previous works (Benkelfat et al., 1995; Javanmard et al., 1999) have described the functional neuroanatomy of CCK-4-induced PA using positron emission tomography (PET) and cerebral blood flow (CBF) measurements. The main objective of the present study was to develop a method to investigate the brain activity pattern related to CCK-4-induced PA in healthy volunteers using functional magnetic resonance imaging (fMRI). Relations between the fMRI patterns and psychological and physiological symptoms of anxiety were investigated. Since anticipatory anxiety (AA) is an intrinsic part of PD (APA, 1994), AA induced by the threat of a CCK-4 readministration was studied in the same way.

Subjects and methods

The study protocol was approved by an accredited independent ethics committee (« Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale » Alsace I, Strasbourg).

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Subjects

Twelve healthy male volunteers, between 18 and 35 years of age (mean age = 27 years, SD = 4), participated in the study after having freely given their written informed consent. They were non-smoker and right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The screening investigations included a physical examination, routine laboratory and alcohol blood tests, urine drug screening, hepatitis and HIV serology, vital signs, electrocardiogram, electroencephalogram, structural magnetic resonance imaging (MRI) and medical history. They had no personal or familial (1st degree) history of psychiatric disorder. In addition, each underwent a psychiatric interview including the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997), the Tridimensional Personality Questionnaire (Cloninger, 1987) and the State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) in order to avoid any subclinical personality or psychiatric disorder that could bias their behavior during the study or make them prone to remote consequences of the challenge. STAI scores between 20 and 39, inclusive, were required to ensure a better homogeneity of the sample. No medication was allowed within 14 days prior to the study onset and during the study period.

Procedure

The study design consisted of two MRI sessions 1 h apart. The first session, which was designed to generate PA, took place at 10 a.m., i.e., at least 2 h after a light standardized breakfast. This session consisted of 2 fMRI scans: the subjects were injected with placebo during the first scan (at 10:15 a.m.) and with CCK-4 during the second one (at 10:30 a.m.), according to an open design. Each scan lasted 10 min, with 3-min recording before injection (baseline, corresponding to the acquisition of 45 functional images) and 7-min recording thereafter (105 images). The placebo scan was intended to assess the possible effects of injection by itself on brain activity. The second scan allowed to study of CCK-4 effects.

The second session was designed to generate AA, and took place 1 h after the end of the first session. It was expected that the subjects who had experienced a PA on CCK-4 would develop AA when threatening with an injection. Consequently, the two sessions, placebo/CCK-4 and AA, were not randomized. The scan took place at 12 a.m. and lasted 13 min, during which blue squares ("rest" periods) and red squares ("threat" periods) were alternatively presented through LCD goggles (Resonance Technology, Inc). Seven blue and six red squares were presented, blue square presentation lasted 68 s (17 images) each and red square presentation 52 s (13 images) each. A timer was displayed during each "threat" period and the subjects were instructed that they could be administered CCK-4 within the last 10 s of the period.

Imaging

Imaging was performed on a 3 T Bruker Medspec 30/90 system (Bruker Biospin, France). A MRI recording session involved recording of pilot images, time series of functional images and anatomical image. Functional images were recorded while the subject was injected with placebo or CCK-4 and during the AA challenge using T2*-weighted multi-slice echo planar imaging (EPI) oriented axially according to the anterior commissure–posterior commissure (AC–PC) line. Standard EPI parameters used were as follows: repetition time (TR) 4 s, echo time (TE) 30 ms, in-plane field of view (FOV) 256 mm, in-plane matrix 64 × 64, slice thickness 4 mm, number of slices 32.

Image processing and statistical analysis

First, raw data were Fourier transformed to produce raw EPI images and the ghosting artifacts were corrected using an on-site reconstruction method (Hennel, 1998).

For placebo and CCK injection scans, EPI images registration was performed using the Medimax freeware (Institut de Physique Biologique, GITIM, Université Louis Pasteur, Strasbourg) in order to optimize motion correction. All functional images were registered to the first functional image in the series using an automated rigid registration algorithm (Nikou et al., 1998). For the AA challenge, EPI images registration was performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Then other EPI image preprocessing and statistical analyses were carried out using SPM2 together with the xjView Toolbox for SPM (http://people.hnl.bcm.tmc.edu/cuixu/xjView/). Preprocessing consisted in normalization of subject's EPI image into the SPM2 brain template and smoothing with an 8 mm FWHM Gaussian filter. For the placebo and CCK-4 time series, period before injection (45 EPI images) and a period corresponding to 20 EPI images after the beginning of injection were modeled as weighted boxcar functions, convoluted with a hemodynamic response function. Difference between periods before and after injection was assessed using the general linear model, yielding t statistics for each voxel. For CCK-4 time series, a second statistical analysis was carried out, using heart rate (HR) as a function of time for the modeling of the data. This analysis method was based on the assumption that if CCK-4 induced a PA, it would happen at the time and with the same time-course than CCK-4 effects on the heart without assuming that HR increase would reflect the anxiety level. The latter allows taking into account that CCK-4 effects were delayed of a few second compared to the 45th volume (onset of injection) resulting from injection duration and the time of appearance of the symptoms. Since no assumptions could either be made concerning PA duration after induction, the whole HR profile could not be used for modeling panic feeling. Therefore, only a part of the measurements were taken into account, from the beginning of the scan to the time corresponding to the half maximum of HR increase, after the maximum HR was reached (Fig. 1). As a mean, a 4.5-min period was analyzed corresponding to 66 functional images. This assumption was also taken into consideration to analyze only 20 volumes after injection in boxcar function model.

For the AA challenge, in the statistical analysis, the beginning and the last seconds of the "threat" period were studied separately. In other experiments, using for example the fear-potentiated startle reflex paradigm (Ross, 1961; Vrana et al., 1988; Vrana and Lang, 1990; Grillon et al., 1991, 1993), it was demonstrated that anticipation was maximum at the time the aversive event was expected. So in the paradigm, the beginning of "threat" periods (corresponding to 9 functional images), the end (4 images) and rest (17 images) were modeled as weighted boxcar functions, convoluted with a hemodynamic response function.

Differences between the beginning of "threat" periods and rest (R_{beg}), end of "threat" periods and rest (R_{end}) and end versus beginning of "threat" periods ($R_{end/beg}$) were assessed using the general

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