Nerve growth factor serum concentrations rise after successful cognitive–behavioural therapy of generalized anxiety disorder

Maria C. Jockers-Scherübl *, Doris Zubraegel, Thomas Baer, Michael Linden, Heidi Danker-Hopfe, Olaf Schulte-Herbrüggen, Peter Neu, Rainer Hellweg

Department of Psychiatry and Psychotherapy, Charité-University Medicine Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany

Abstract

Generalized anxiety disorder (GAD) is a chronic stress disease with permanent physical tension and cognitive strain. Raised nerve growth factor (NGF) serum levels were reported as an acute stress reaction in soldiers before their first parachute jump even before the rise in cortisol. Taking GAD as a clinical model of chronic stress, we measured NGF in the serum of 22 patients with GAD before and after cognitive–behavioural therapy (CBT) and compared them to those of healthy normal controls. Treatment response was tested by the values of the State and Trait of Anxiety Inventory (STAI) and the Hamilton Anxiety Scale (HAM-A) as treatment outcome variables. The NGF values of patients and controls were similar at baseline ($p=0.8941$); however, with successful treatment, corresponding to a mean reduction in the HAM-A by more than 50% and a reduction in the clinical global impression scale (CGI) median from 4 to 1, the patients' NGF serum concentrations rose significantly ($p=0.0006$) which might correspond to an altered stress reaction, possibly contributing to good therapeutic response with CBT. There were 3 patients with a HAM-A decrease of less than 15%. In those patients NGF rose only marginally. Hence, the increase in serum NGF seems to indicate good treatment response.

1. Introduction

Generalized anxiety disorder (GAD) is a chronic and disabling mental disease, occurring four times more frequently in women than in men. It causes severe distress and interferes with daily functioning since worry is present most of the time (American Psychiatric Association, 1994). GAD is often associated with depressive illness and has increasingly become a focus of scientific interest (Fricchione, 2004; Hunt et al., 2004; Mogg et al., 2004; Stein, 2004; Surtees et al., 2003). Apart from antidepressants, cognitive–behavioural therapy seems to be the best therapy option and has been tested recently in a manualised form in Germany (Linden et al., 2005).

The classical role attributed to the neurotrophin nerve growth factor (NGF) is its neurotrophic function within the central and peripheral nervous system where NGF acts predominantly as a survival factor during development and as a maintenance of function factor during adult life (for reviews see Hellweg et al., 1998; Thoenen et al., 1987). Additionally there is increasing evidence that NGF has multiple immunomodulatory functions, similar to a cytokine and can be raised in stressful situations (Lang et al., 2004b; Levi-Montalcini et al., 1996). In accordance with this observation, raised NGF serum concentrations have been found in soldiers before and after their first parachute jump, thus representing an effect of acute cognitive stress (before) and also physical stress (the jump itself) on the NGF serum level (Aloe et al., 1994). In GAD apprehensive expectation is usually present, combined with physical tension and its sequelae, leaving most patients feeling chronically stressed

(American Psychiatric Association, 1994). The disease is therefore a valid model for chronic stress, including cognitive as well as physical parameters.

We measured NGF serum levels in patients with diagnosed GAD according to DSM-IV (American Psychiatric Association, 1994) before and after treatment with 25 sessions of manualised cognitive–behavioural therapy (CBT) on the hypothesis of change in NGF levels with reduced subjective stress after successful treatment.

2. Method

The study was conducted within the framework of a study evaluating manualised cognitive–behavioural therapy in patients suffering from GAD alone, funded by the German Research Council (Linden et al., 2005). Approval for the study was obtained from the institutional board (local ethics committee) and each proband gave written informed consent before participating in the study.

2.1. Patient population

Patients between 18 and 65 years of age suffering exclusively from GAD according to DSM-IV were included into the study if they agreed to the additional drawing of blood before and after the completion of psychotherapy treatment. Any other comorbid psychiatric or somatic disorder led to exclusion in order to minimize confounding factors with respect to the success of the CBT and to the height of the NGF levels. Pharmacotherapy was not allowed at any time during the CBT treatment period. No patients with benzodiazepine treatment within three months prior to beginning of the study were included because withdrawal symptoms can potentially alter NGF values. No patient had had a psychotherapeutic treatment prior to this study. At the index evaluation (T_0) patients were rated with the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959), the clinical global impression scale (CGI; National Institute of Mental Health, 1996) and the self-rating instrument State and Trait of Anxiety Inventory (STAI; Spielberger et al., 1983). Behavioural scores are shown as mean number of points (sum of scores) and standard deviation (S.D.). The CBT was carried out by experienced psychotherapists in CBT and after two trial sessions 25 sessions of CBT according to a standardised manual followed (Barlow et al., 1992; Zubrägel and Linden, 2000). After ending the therapy (T_{25}) patients were rated again with the above named scales. All the ratings were done by two experienced psychologists not involved in the treatment of the patients. Good treatment response was defined as more than a 50% reduction in the individual HAM-A score of every subject (maximum possible score as sum of the 14 different items amounts to 56) from baseline to end of treatment.

The healthy control subjects were mainly recruited from the hospital staff or personally known to them. In order to exclude any somatic or psychiatric lifetime diagnosis an extensive interview was carried out and the Mini-International Neuropsychiatric Interview (M.I.N.I., Sheehan et al., 1998) was car-

ried out. Present or past medication or psychotherapy for any reason led to exclusion from the study.

2.2. CBT treatment in brief

The cognitive–behavioural treatment was based on the methods described in manuals by Linden et al. (1995) and Zubrägel and Linden (2000) with reference to Barlow et al. (1992). Apart from general strategies of cognitive–behavioural therapy including progressive muscle relaxation techniques, problem solving, or planning recreational activities, the main focus of the treatment was to control and change worrying and catastrophizing anticipations.

2.3. NGF measurements

Patients were placed in a quiet environment and 5 ml blood was drawn before the beginning of treatment (T_0) and after its ending (T_{25}); it was centrifuged immediately after withdrawal for 15 min at 3500 rev/min at room temperature. Serum was then stored at $-20\ °C$ until use. NGF concentrations in the re-thawed serum were determined by a highly sensitive and specific fluorometric two-site ELISA with a detection limit of 1 pg/ml NGF described in detail elsewhere (Hellweg et al., 1989; Lang et al., 2003). NGF serum values are shown in pg/ml (mean values±S.D. and median plus interquartile range). Additionally, blood was drawn in 16 healthy control subjects and treated likewise.
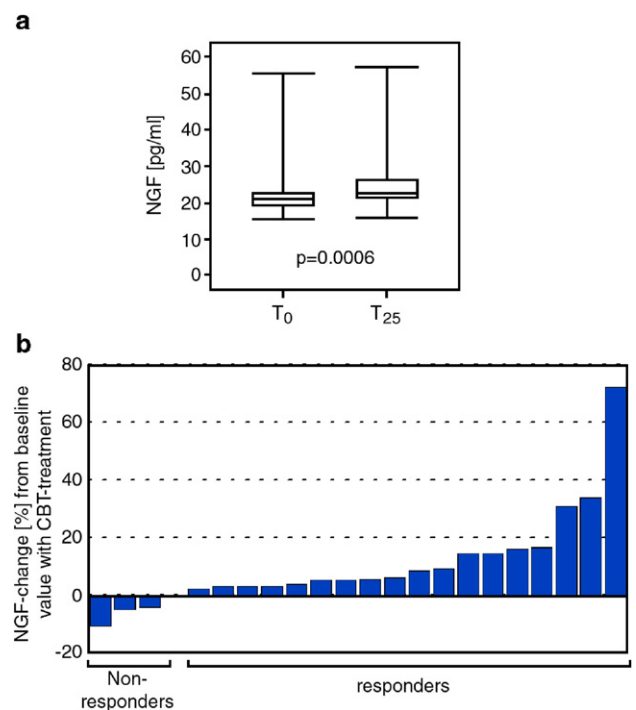
Fig. 1. (a) Changes in serum NGF from baseline (T_0) to end of treatment after 25 sessions of CBT (T_{25}) in GAD patients as a box- plot-diagram with statistical significance given as insert. (b) Diagram showing the individual changes of NGF in percent from T_0 to T_{25} grouped as therapy responders and non-responders (i.e. 15% or less change in HAM-A from Baseline to end of treatment). CBT=cognitive–behavioural therapy; NGF=nerve growth factor; HAM-A=Hamilton Anxiety Scale.