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Improvement of working but not declarative memory is correlated with HPA normalization during antidepressant treatment

Astrid W. Zobel*, Svenja Schulze-Rauschenbach, Olrik C. von Widdern, Martin Metten, Nikolaus Freymann, Katja Grasmäder, Ute Pfeiffer, Susanne Schnell, Michael Wagner, Wolfgang Maier

Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universitätsklinikum Bonn, Sigmund-Freud-Straße 25, Bonn 53105, Germany

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Abstract

Previous research demonstrated that depression is associated with hyperactivity of the hypothalamus–pituitary–adrenocortical (HPA) system after stimulation. There is also strong evidence that the modulation of corticosteroids in the brain induces memory dysfunction which represents core features of depression. Antidepressant treatment with serotonin reuptake inhibitors (SSRIs) alleviates both dysfunctions. Thus, these previous observations propose a correlation between treatment induced changes of the endocrinological response of the HPA system to challenge with dexamethasone and CRH and changes of memory functions during antidepressant treatment. This study explores the relationship between depression, memory functions and the responsiveness of the HPA system as assessed by the combined DEX/CRH test during antidepressant treatment in $n = 64$ patients with major depression during a four weeks treatment with citalopram. We found that treatment induced changes of the cortisol response pattern in the DEX/CRH test were correlated with improvement of working memory but not so with episodic memory, sustained attention or global severity of depression. We suggest that improvement of working memory is more sensitive to the changes of hormones of the HPA system (e.g. cortisol) than other cognitive functions and the global severity of depression.

Keywords: HPA; DEX/CRH; Cortisol; Working memory; Cognitive function; Depression; Treatment

1. Introduction

Dysfunction of the hypothalamus–pituitary–adrenocortical (HPA) system is a consistent feature of depression: an insufficient feedback mechanism of the central corticosteroid receptor is hypothesized to induce the hyperactivity of the HPA system (Holsboer, 1998; Holsboer, 2000). There is strong evidence that dysfunction of this system contributes to the symptoms of depression and normalizes during successful antidepressant treatment.

Although it has been assumed that the HPA dysfunction is part of the underlying pathophysiology the relationship to clinical features of depression is complex. Three examples: (1) The crossectional correlation between the global severity of the clinical syndrome and the pathophysiological basis of depression is only weak or modest (Hatzinger et al., 2002); multiple intervening and modulating factors (e.g. psychosocial support and stimulation) might explain the inconsistent relationship. (2) Although initial HPA dysregulation is gradually reduced during successful antidepressant treatment (Heuser et al., 1996; Holsboer-Trachsler et al., 1990) the magnitude of this change is only weakly related to the magnitude of the simultaneous clinical improvement. (3) HPA overdrive might continue despite of clinical remission; this constellation indicates a higher risk for relapse within six months (Zobel et al., 1999; Zobel et al., 2000). Therefore, HPA activity is rather a valid indicator of stability of clinical remission than a crossectional correlate of the severity of depression.

* Corresponding author. Tel.: +49-228-2-87-5717; fax: +49-228-2-87-4760.
E-mail address: astrid.zobel@ukb.uni-bonn.de (A.W. Zobel).

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Depression is not only a disturbance of mood and drive. A more directly brain related core feature of depression are cognitive dysfunction (Austin et al., 2001). Several studies have found impairments of memory and attention (Hemmeter et al., 2000) in depression. Multiple memory systems are involved depending on the subtype of depression: there is strong evidence of episodic memory dysfunction in depression; this memory function relies preferentially on the integrity of hippocampal functions. Working memory impairments were consistently reported only in severe or moderate depression; in contrast to episodic memory working memory depends heavily on the integrity of prefrontal brain areas (Austin et al., 2001; Pelosi et al., 2000). The relationship of these cognitive brain functions to the pathophysiological basis of depression might be stronger than of the clinical symptoms of behavior and mood.

One reason for this suggestion is that memory functions can be modulated by hormones of the HPA system. Previous studies using the dexamethasone suppression test report verbal memory deficits among non-suppressors with depression (Wolkowitz et al., 1990). A recent report (Hemmeter et al., 2000) found that overresponsivity of the HPA system was associated with a reduced amplitude of the contingent negative variation which may induce cognitive impairments. Beyond these few studies in depressed patients most evidence for the influence of change of HPA hormones in the brain on memory functions comes from studies in healthy humans and animals: The elevation of circulating glucocorticoids was strongly correlated with impairments of multiple memory functions during the encoding, the consolidation and the retrieval phase in episodic as well as working memory (Lupien and McEwen, 1997; Newcomer et al., 1999; Austin and Mitchell, 1995; Al'absi et al., 2002). In particular CRH impacts on memory and cognition (Zorrilla et al., 2001).

During successful antidepressant treatment cognitive impairment resolves (Koetsier et al., 2002) and the HPA abnormalities are gradually reduced (Zobel et al., 2000). Given a consistent crossectional relationship between the hyperactivity of the HPA system and memory functions in non-depressed subjects it can be expected that: (1) the endocrinological and memory changes are going together during antidepressant treatment, (2) this correlation is not mediated by improvement in other cognitive dimensions as attention and concentration and (3) the correlation of the endocrinological alterations with changes of memory functions is closer than with changes in the global severity of depression.

We explored these hypotheses in a sample of moderately to severely depressed inpatients under four-weeks standard fixed dose treatment with citalopram. The combined DEX/CRH test was applied as the most sensitive indicator of the HPA dysregulation in depression (Holsboer, 2000). We focus on two main components of the memory system: working memory by the Digits Backward test and episodic memory by a German version of the Rey Auditory Verbal Learning Test (VLMT). In order to control for the more unspecific cognitive functions and their changes during treatment we also used a test for sustained attention (d2 test).

2. Methods

2.1. Patients, treatments and time points of measurement

$n = 82$ consecutively admitted inpatients (mean age 46.6 ± 14.6 years, range 19–65 years) with the diagnosis of unipolar recurrent major depression and a current major depressive episode (DSM-IV) without psychotic symptoms were included into the study. Patients with serious somatic diseases, substance related disorders or treated with mood stabilizers were excluded. Suicidal attempts or serious suicidal ideation were also reasons for exclusion from the study. Patients with severe agitation syndrome were excluded as they were treated by sedative antidepressants. As psychotic major depression is endocrinologicaly different from non-psychotic depression (Belanoff et al., 2001), we excluded patients with psychotic features. The diagnosis was verified by clinical expert diagnosis as well as by the structured clinical interview SKID. Severity of depression was assessed by application the Hamilton Rating Scale for Depression (HAMD) with 17 items. For inclusion a minimal level of severity of depressive symptomatology was requested (HAMD score >18) for day 0 and one week later (day 8).

Patients received a standardized antidepressant pharmacological treatment as administered within an internal quality assurance program according to clinical guidelines:

(a) citalopram (precondition: no severe agitation),
(b) fixed dosage after day 4 to day 36,
(c) stepwise increase of dosage to 20, 30 or 40 mg citalopram from day 1 to day 4 (dosage by clinical decision),
(d) as adjunct psychotropic treatment only lorazepam up to 3 mg with fixed dose from day 4 to day 36 (other psychotropic medication was not prescribed).

18 patients could either not continue with the allocated medication because of side effects, emergence of psychotic symptoms, non-compliance in treatment or rejection of the neuropsychological or neuroendocrinological follow-up examination. Thus we analyze the completed treatment results of 64 patients.

The mean citalopram dosage was 28.1 ± 6.5 mg. $n = 37$ of the 64 patients received lorazepam with a mean dosage of $1.4 \pm .9$ mg.

Other medications because of other medical conditions were prescribed in 24 patients (e.g. antihypertensiva) and remained unchanged between t1 and t2.