

Review article

The combined dexamethasone/CRH test as a potential surrogate marker in depression

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Abstract

There is compelling evidence that impaired corticosteroid receptor function is the key mechanism in the pathogenesis of depression resulting in a dysfunctional stress hormone regulation, which can be most sensitively detected with the combined dexamethasone (dex)/corticotropin releasing hormone (CRH) test. Treatment with different kinds of antidepressants is associated with a reduction of the hormonal responses to the combined dex/CRH test suggesting normalization of impaired corticosteroid receptor signaling as the final common pathway of these drugs. Consequently, the combined dex/CRH test is suggested as a screening tool to decide whether new compounds designed as antidepressants provide sufficient efficacy to normalize corticoid receptor signaling in depressed patients. We summarize own data and findings from the literature suggesting that (1) the neuroendocrine response to the combined dex/CRH test is elevated during a major depressive episode, but (2) tends to normalize after successful treatment. (3) Favorable response to antidepressant treatment can be predicted by determining the dex suppressor status on admission. For optimal prediction of non-response to antidepressant treatment, however, the results of a second dex/CRH test are necessary. These findings, together with the fact that impaired corticosteroid receptor signaling is considered as key mechanism of the pathogenesis in depression, support the suitability of the combined dex/CRH test as a surrogate marker for treatment response in depression. In conclusion, the combined dex/CRH test is a promising candidate to serve as a screening tool for the antidepressive effects of new compounds in clinical drug trials. Furthermore, the test appears to be capable of predicting the individual likelihood to respond to a current antidepressant treatment. If a drug treatment fails to normalize the outcome of the combined dex/CRH test, a change of the treatment strategy is recommended. Further systematic research is required and already ongoing to confirm the suitability of the combined dex/CRH test as a surrogate marker in depression.

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Keywords: Depression; Dex/CRH test; Drug screening; HPA system; Response prediction; Surrogate marker

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Abbreviations: ACTH, adrenocorticotrophic hormone; CRH, corticotropin releasing hormone; dex, dexamethasone; GR, glucocorticoid receptor; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamus–pituitary–adrenal; MDE, major depressive episode; 5-HT, 5-hydroxytryptamine, serotonin.

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1. Introduction

Affective disorders have been recognized as one of the most common medical conditions world wide with an average 12-month prevalence of 10% and an average life time prevalence of 17% in the United States (Kessler et al., 1994). When considering direct medical costs and indirect economic losses due to missed work days and decreased income, depression takes a major share of the overall health-care expenditures in industrialized countries (Simon et al., 1995; Thompson and Richardson, 1999).

A large number of antidepressants with different pharmacological properties are available, which show similar efficacy in the treatment of affective disorders (Nierenberg, 1994; Simon, 2002). A major drawback of all these antidepressants is the delayed onset of clinical action which takes several weeks or even months (Quitkin et al., 1996). The reason for this delay is the mode of action of these drugs, i.e., the modification of the serotonergic and/or noradrenergic neurotransmission, which seems to be remote from the actual neurobiological process leading to symptom resolution. We will argue that a restoration of corticosteroid receptor function resulting in a normalization of the hypothalamus–pituitary–adrenocortical (HPA) system regulation is the proximal mediator for the clinical action of antidepressant drugs. Consequently, the degree of normalization of the HPA system should surrogate the clinical efficacy of a drug in antidepressant treatment trials. Furthermore, we will show that normalization of the HPA system regulation precedes clinical improvement. Therefore, normalization or the persistency of altered HPA system function during treatment is assumed to predict response or non-response to the current antidepressant medication.

According to the results of controlled treatment trials about 50% of depressed patients fail to respond to the treatment with tricyclic antidepressants or serotonin reuptake inhibitors (Nelson, 1998). These patients require a change of the treatment strategy, either by increasing the dose, by combining or augmenting with another medication, or by switching to another antidepressant. Since the time until the onset of antidepressant effects takes at least several weeks, the failure to respond to the initial medication or even to further treatments results in a marked extension of the illness episode. Therefore, surrogate markers predicting non-response at the earliest possible time are needed to avoid leaving patients under an inefficient medication and to save direct and indirect costs for the health care system, e.g., by reducing hospitalization times.

Among neuroendocrine parameters, measures of the HPA system are most promising for the prediction of treatment response in depression, since HPA system alterations during an acute episode and its normalization after successful treatment are the most consistently observed laboratory findings in patients with affective disorders (Holsboer and Barden, 1996; Holsboer, 2000; Pariante et al., 2004; Raison and Miller, 2003). Holsboer et al. (1987) proposed a

combined dexamethasone (dex)/corticotropin releasing hormone (CRH) test for the assessment of HPA system function in psychiatric disorders, which is the most sensitive tool for the detection of HPA system alterations (Heuser et al., 1994) and which is refractory against most disease-unrelated factors like caffeine and nicotine consumption, body weight, and acute stressors during the test (Künzel et al., 2003).

After an introduction to the corticosteroid receptor hypothesis of depression we summarize own results and data from the literature indicating that change in the outcome of combined dex/CRH tests reflects the effects of antidepressants and predicts the course of treatment response in depression. The suitability of the combined dex/CRH test to serve as a potential surrogate marker for the assessment of clinical drug efficacy and for the prediction of treatment response is discussed.

2. The corticosteroid receptor hypothesis of depression

The most consistent laboratory finding in depression is an impaired regulation of the hypothalamus–pituitary–adrenocortical (HPA) system during an acute episode and its normalization after successful treatment (Holsboer and Barden, 1996; Holsboer, 2000; Pariante et al., 2004; Raison and Miller, 2003). The dexamethasone suppression test (DST), an established measure for the detection of functional alterations in the HPA system, was suggested to predict the clinical course in depressed patients (Holsboer et al., 1982; Holsboer, 1983). If the DST result is initially abnormal (i.e., showing inadequate cortisol non-suppression after dexamethasone treatment), a normalization occurs usually during successful antidepressant treatment. In a majority of studies, failure to normalize was associated with poor outcome and early relapse (Greden et al., 1983; Holsboer et al., 1982; Ribeiro et al., 1993).

In healthy subjects dexamethasone peripherally suppresses ACTH and cortisol release by binding to glucocorticoid receptors (GR), which inhibit the synthesis and secretion of ACTH and, consequently, the secretion of cortisol. The escape from the suppressive effects of dexamethasone in patients with affective disorders can be explained by impaired GR signaling in these patients. This is supported by preclinical findings. Barden et al. developed a transgenic mouse model with a primary defect of the glucocorticoid receptor (GR) (Pepin et al., 1992b). The model was designed as a partial “knock down” of the GR gene by incorporating a gene fragment into the mouse genome inducing the expression of GR antisense RNA, which results in decreased levels of original GR mRNA. This transgenic mouse model mimics conditions that are assumed to be responsible for an elevated neuroendocrine response to the DST in depressed patients. In line with this assumption, Stec et al. (1994) observed a profound escape from dex suppression in GR antisense transgenic mice, which normalized after 10 days of treatment with the antidepressant desipramine (Pepin et al., 1992a).

Lack of sensitivity of the DST has been frequently criticized. Arana and Ornstein (1985) reviewed the DST in more than 5000 depressed patients and reported an overall sensitivity of only about 44%. To overcome this limitation, a combined dexamethasone (dex) suppression/corticotropin releasing hormone (CRH) stimulation test was proposed by Holsboer et al. (1987). This test is sensitive to impaired GR signaling at the pituitary level as well as to the effects of increased secretions of central neuropeptides, especially CRH and vasopressin, which are a consequence of impaired central GR signaling (Holsboer and Barden, 1996; Holsboer, 2000; Keck and Holsboer, 2001). Vasopressin, which is co-secreted from hypothalamic CRH neurons, amplifies the effects of CRH at the pituitary level (Scott and Dinan, 2002) and contributes to elevated ACTH and cortisol responses to the combined dex/CRH test in depression. This could be demonstrated by von Bardeleben et al. (1985) who observed elevated plasma ACTH and cortisol levels similar to those in depression when vasopressin was infused at a low rate concurrently with CRH in dexamethasone pretreated controls.

Superior sensitivity of the combined dex/CRH test compared to the DST was repeatedly confirmed, e.g., for patients suffering from a major depressive episode (Heuser et al., 1994; Deuschle et al., 1998), from bipolar disorder (Rybakowski and Twardowska, 1999), and from chronic depression (Watson et al., 2002). Hatzinger et al. (1996) developed an adaptation of the combined dex/CRH test for rats. They administered 30 µg/kg body weight dex at noon and infused 50 ng/kg body weight CRH at 8 pm and observed elevated ACTH and corticosterone responses in aged male Wistar rats, which normalized when a vasopressin receptor 1 (V1) antagonist is infused prior to CRH stimulation (Hatzinger et al., 2000). No effects of the V1 antagonist were found in young control rats.

Keck et al. (2002) conducted the combined dex/CRH test in two Wistar rat lines selectively bred for high innate (HAB) and low innate anxiety related behavior (LAB), respectively. Male HAB but not LAB rats showed elevated ACTH and corticosterone responses to the combined dex/CRH test. When male HAB rats were treated with a V1 antagonist prior to CRH stimulation, ACTH and corticosterone responses were markedly reduced. Same effects were observed after chronic treatment with the selective serotonin reuptake inhibitor paroxetine which was accompanied by a normalization of AVP gene expression in the hypothalamic paraventricular nucleus in HAB rats (Keck et al., 2003).

In conclusion, clinical and preclinical results support the concept of impaired corticosteroid receptor function as the key mechanism in the pathogenesis of depression resulting in a dysfunctional regulation of the HPA system, which can be sensitively measured by the combined dex/CRH test. A variety of drugs directly aiming at receptors involved in the stress hormone regulation like corticotropin releasing hormone (CRH) receptor 1 antagonists, GR antagonists or

vasopressin receptor 1 antagonists are currently under development. Preliminary clinical studies suggest therapeutic efficacy for the CRH R1 antagonist NBI 30775 (Zobel et al., 2001) in major depression and for the GR antagonist C-1073 in psychotic depression (Belanoff et al., 2002). It is hypothesized that these drugs provide a faster onset of their clinical efficacy since they act at structures that are assumed to be more proximally involved in the resolution of depressive symptoms.

3. The combined dex/CRH test in depression

The procedure of the combined dex/CRH tests was described in detail elsewhere (Holsboer et al., 1987; von Bardeleben and Holsboer, 1989; Heuser et al., 1994). Briefly, 1.5 mg dexamethasone is orally administered at 11 pm the day before stimulation with 100 µg human CRH. In the short version of the test Heuser et al. (1994) suggested that blood samples are drawn at 3:00, 3:30, 3:45, 4:00, and 4:15 pm. CRH is injected within 30 s, just after the 3:00 pm sample is collected. The subjects rest supine throughout the test. Plasma cortisol and ACTH concentration of the first specimen collected at 3:00 pm reflect the suppressive effects of the dexamethasone application at 11 pm the day before, whereas the other four samples reflect the response to the CRH injection.

Elevated plasma cortisol responses to the combined dex/CRH test could be observed in most studies with patients during an acute major depressive episode (Holsboer et al., 1987; von Bardeleben and Holsboer, 1989, 1991; Holsboer-Trachsler et al., 1991; Heuser et al., 1994, 1996; Modell et al., 1997; Kunugi et al., 2004). Minor or no alterations of the HPA system were found in dysthymic or chronically depressed patients (Oshima et al., 2000; Watson et al., 2002). Elevated hormonal responses to the combined dex/CRH test do not uniquely characterize depression, but can also be observed during an acute manic condition (Schmider et al., 1995), in anxiety disorders (Schreiber et al., 1996), in borderline patients with a history of chronic childhood abuse (Rinne et al., 2002), and in schizophrenic patients (Lammers et al., 1995). However, most pronounced alterations of the HPA system among psychiatric patients are found in patients suffering from unipolar or bipolar affective disorders (Joyce and Paykel, 1989).

In a study with 235 acutely depressed in-patients we demonstrated that the plasma cortisol response to the combined dex/CRH test is relatively refractory against the effects of most disease-unrelated factors like caffeine and nicotine consumption, acute stressors, weight, and age (Künzel et al., 2003). Only female gender was weakly correlated with the neuroendocrine test response. The kind of antidepressant treatment or intake of benzodiazepines do not affect the outcome of the test (Künzel et al., 2003; Zobel et al., 2001). Exceptions are the mood stabilizers lithium and carbamazepine that interfere with plasma ACTH and

cortisol concentrations at baseline and under stimulation conditions (von Bardeleben et al., 1988; Bschor et al., 2002), presumably by stimulating the release of vasopressin (lithium) and by affecting the metabolism of dexamethasone (carbamazepine).

It can be concluded that alterations of the HPA system during an acute depressive episode can be most sensitively detected by the combined dex/CRH test. Elevated neuroendocrine response to the combined dex/CRH test, however, cannot be regarded as specific to depression since other psychiatric disorders as well as medical disorders like Cushing's disease (Yanovski et al., 1993, 1998) and neurological disorders like multiple sclerosis (Grasser et al., 1996; Then-Bergh et al., 1999, 2001) are associated with an elevated response to this test.

4. Dex/CRH test as surrogate marker for drug efficacy

In a number of studies the combined dex/CRH test was conducted before and after initiation of an antidepressant treatment. Although the design of the studies and the kind of medication vary, most results indicate a normalization of the neuroendocrine response to the combined dex/CRH test. This could be shown for tricyclic antidepressants (Holsboer et al., 1987; Holsboer-Trachsler et al., 1991; Heuser et al., 1996; Deuschle et al., 1997; Frieboes et al., 2003), for selective serotonin reuptake inhibitors (Nickel et al., 2003; Rinne et al., 2003), for a selective serotonin reuptake enhancer (tianeptine; Nickel et al., 2003), and for a combined $\alpha_2/5$ -HT_{2/3}/H₁ receptor antagonist (mirtazapine; Schüle et al., 2003). Preclinical studies found that different types of antidepressants increase glucocorticoid receptor (GR) gene expression and enhance GR sensitivity (Holsboer and Barden, 1996; Holsboer, 2000; Raison and Miller, 2003).

This is in line with preclinical data showing normalization of the HPA system function in a GR antisense transgenic mouse model after treatment with a reversible inhibitor of monoamine oxidase type A (moclobemid, Montkowski et al., 1995) and with tricyclic antidepressants (amitriptyline, Barden, 1996; desipramine, Pepin et al., 1992a). Normalized neuroendocrine responses to an adaptation of the combined dex/CRH were also found in rats selectively bred for high innate anxiety after chronic treatment with a selective serotonin reuptake inhibitor (paroxetine, Keck et al., 2003).

Clinical and preclinical data support the assumption of a normalization of impaired corticosteroid receptor signaling as the final common pathway of antidepressants with different pharmacological profiles. This is illustrated in Fig. 1.

As a consequence, clinically effective antidepressants should be capable to normalize dysregulation of the HPA system in patients with initially elevated neuroendocrine response to the combined dex/CRH test. Therefore, we suggest the combined dex/CRH test as a surrogate marker for clinical efficacy in drug development. A new drug can be considered as clinically effective if its application in depressed patients with initially altered neuroendocrine responses to the combined dex/CRH test leads to a normalization of the test indicating that treatment with the drug resolves impaired corticosteroid receptor signaling in these patients.

5. Dex/CRH test as surrogate marker for treatment response

A limited number of studies are available examining the associations between neuroendocrine responses to the

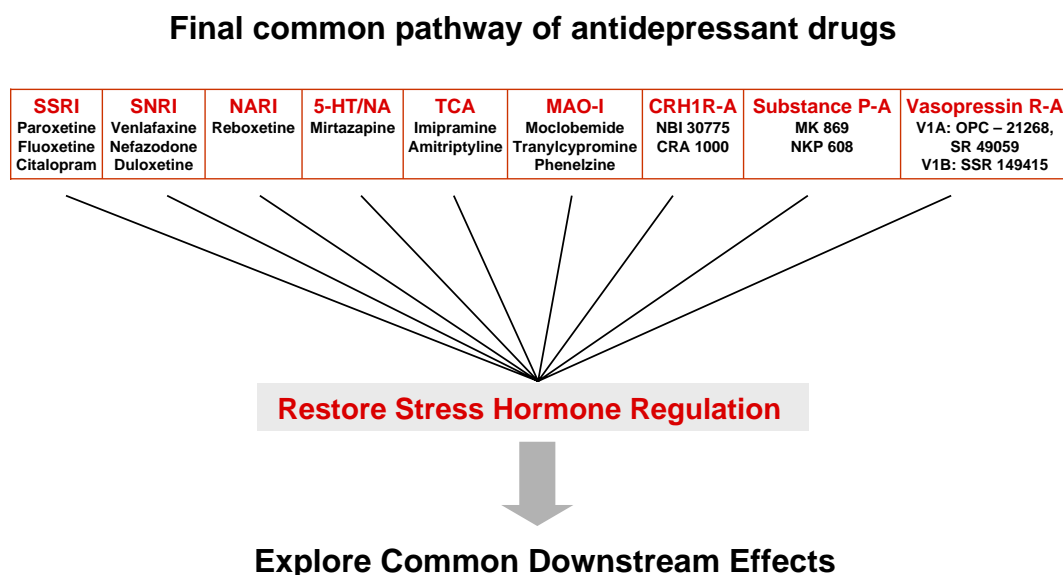


Fig. 1. Restoration of the stress hormone regulation is suggested as the final common pathway of antidepressant drugs.

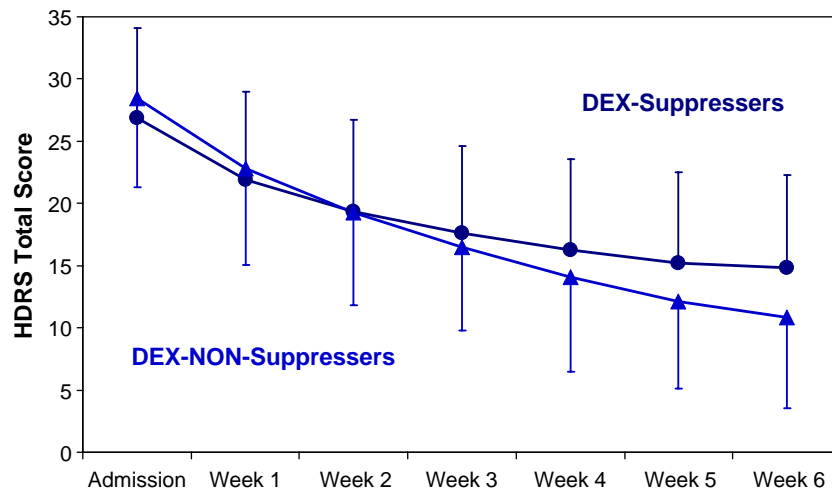


Fig. 2. Change of HDRS total scores (mean±S.D.) during the first 6 weeks of treatment differs between dex suppressors ($n=176$, circles) and dex non-suppressors ($n=35$, triangles) ($p<0.001$).

combined dex/CRH test and the subsequent course of depressive symptoms. In one study plasma cortisol levels in the combined dex/CRH test predicted clinical response to fluoxetine treatment in 12 male depressed patients (Deuschle and Heuser, unpublished). In another study elevated plasma ACTH but not cortisol responses were associated with unfavorable outcome of a 6-week treatment trial with trimipramine (Holsboer-Trachsler et al., 1994). Bschor et al. (2002) examined 30 treatment resistant patients with unipolar depression and did not find differences in ACTH and cortisol response to the combined dex/CRH test between responders and non-responders to a 4-week lithium augmentation trial. However, they observed an elevated cortisol to ACTH peak ratio indicating an enhanced sensitivity of the adrenal cortex in non-responding patients (Bschor et al., 2003). No associations between dex/CRH test outcome and treatment response were reported by Deuschle et al. (1997), Nickel et al. (2003), and Schüle et al. (2003).

Regarding our own results collected with more than 250 depressed inpatients, we do not find significant associations between the cortisol response to a combined dex/CRH test conducted during the first 2 weeks after admission to the hospital and the subsequent course of psychopathological symptoms under naturalistic conditions. However, we found that post dex ACTH and cortisol levels (baseline) prior to stimulation with CRH anticipates subsequent treatment response. As proposed by Heuser et al. (1994), we separated the total group of patients in sub-samples of dex suppressors and dex non-suppressors according to the baseline cortisol levels. We selected 27.5 ng/ml as cutoff, which corresponds to the criterion suggested by Heuser et al. (1994).¹ 80% of

the patients were dex suppressors, 20% were dex non-suppressors. Although these two groups did not differ in age, gender distribution, or psychopathology, they showed substantial differences in the course of the psychopathology ($p<0.001$). In Fig. 2 the change of the total score of the Hamilton Depression Rating Scale (HDRS) in dex suppressors and non-suppressors is depicted.

Our data suggest that dex non-suppression is associated with a favorable treatment outcome after 6 weeks. There are several other studies supporting the notion of a better treatment response in dex non-suppressors, but the overall evidence that dex suppressor status predicts treatment response is weak. There is, however, more agreement that the degree of cortisol suppression by dexamethasone characterizes biologically distinct subgroups of patients (Gitlin and Gerner, 1986; Holsboer and Barden, 1996; Ribeiro et al., 1993). Therefore, we analyzed treatment response separately for dex non-suppressors and suppressors. After this separation, we observed a distinct association between high plasma cortisol response to the combined dex/CRH test (area under the cortisol curve, AUC) and poor treatment response in dex non-suppressors (time until stable response ($\text{HDRS} \leq 50\%$)/stable remission ($\text{HDRS} < 10$): $r=0.32/0.49$, $p=0.023/0.002$), and a weaker but significant association between high cortisol response to the combined dex/CRH test (AUC) and poor treatment response in dex suppressors (low speed of improvement: $r=0.18$, $p=0.012$).

Summarizing our results, the post dex ACTH and cortisol levels and the dex suppression status on admission are associated with clinical response after 6 weeks of treatment. After separating patients according to their degree of dexamethasone induced plasma cortisol suppression, high cortisol responses to the combined dex/CRH are significantly associated with poor clinical response in dex non-suppressors (time until stable response and remission) and in dex suppressors (low

¹ Due to a linear bias in the RIA detection system, previous cortisol results from the laboratory of our institute were artificially elevated. The DEX suppressor threshold reported by Heuser et al. (1994) was derived from a normative database from the same laboratory before the bias was detected. The bias corrected threshold was set to 27.5 ng/ml.

speed of improvement). The results of a single dex/CRH test, however, do not provide sufficient information for a sensitive prediction of treatment outcome in depression. Repeated tests are required evaluating whether HPA system alterations persist or normalize during antidepressant treatment (Holsboer et al., 1987; Ribeiro et al., 1993; Zobel et al., 2001).

Our own data from the Munich Antidepressant Response Signature (MARS) project comprise 64 depressed patients with a combined dex/CRH test during the first week after admission and a second dex/CRH test between 2 and 3 weeks later (unpublished data). In these patients, psychopathology was assessed weekly with the HDRS. After 6 weeks of antidepressant treatment, 36 patients (56%) responded ($\Delta\text{HDRS} \leq 50\%$), and 28 of them (78%) showed remission of symptoms ($\text{HDRS} < 10$). In 28 depressed patients HDRS scores were available during a treatment period of 10 weeks with a second dex/CRH test conducted on average about 5 weeks after the first dex/CRH test on admission. 19 of these patients responded (68%) after 10 weeks, but only 11 of them (58%) achieved remission ($\text{HDRS} < 10$). We calculated the relative risk and the odds ratio for response after 6 and 10 weeks of treatment separately for the dex suppresser status (dex suppression vs. dex non-suppression) on admission, for the change of the cortisol response to the second dex/CRH test (reduction vs. no reduction of the cortisol response), and for both predictors combined. Both predictors contribute equivalently to the prediction of treatment response after 6 and 10 weeks. Dex suppression on admission as well as the persistency of elevated plasma cortisol levels in the second dex/CRH test resulted in a two-fold higher risk not to respond after 6 weeks and in a four- to five-fold higher risk after 10 weeks, respectively. However, dex suppression on admis-

sion seems to be superior for the prediction of response indicated by a higher rate of correctly classified responders, while persistency of high cortisol levels in a second dex/CRH test provides higher sensitivity for the prediction of non-response when the rate of correctly classified non-responders are compared. We combined both predictors and attributed dex non-suppression on admission to the prediction of a favorable response and the persistency of elevated cortisol levels in the second dex/CRH test to the prediction of non-response. The combination of both predictors led to substantially higher odds ratios and to higher relative risk rates for the failure to respond after six ($\text{RR}=3$) and 10 weeks ($\text{RR}=6$). Significant associations were also obtained for remission ($\text{HDRS} < 10$) after 6 ($p=0.037$) and 10 weeks ($p=0.040$) as outcome criterion. However, the results were less pronounced indicating that further factors contribute to the question of whether patients, who responded to antidepressant treatment, achieve full remission of symptoms.

In Fig. 3 the HDRS scores between admission and week 10 are depicted in patients with a favourable (dex non-suppression on admission) and with a poor response prognosis (persistently elevated cortisol responses to the second dex/CRH test).

The association between response prognosis derived from the combined dex/CRH tests and change in psychopathology is highly significant ($p < 0.001$). It can be concluded from these observations that patients who do not show a reduction of the cortisol response to a second dex/CRH test require a change of the treatment strategy, e.g., by increasing the dose, by combining or augmenting with another medication, or by switching to another antidepressant, since they are unlikely to show clinical response under the current antidepressant treatment.

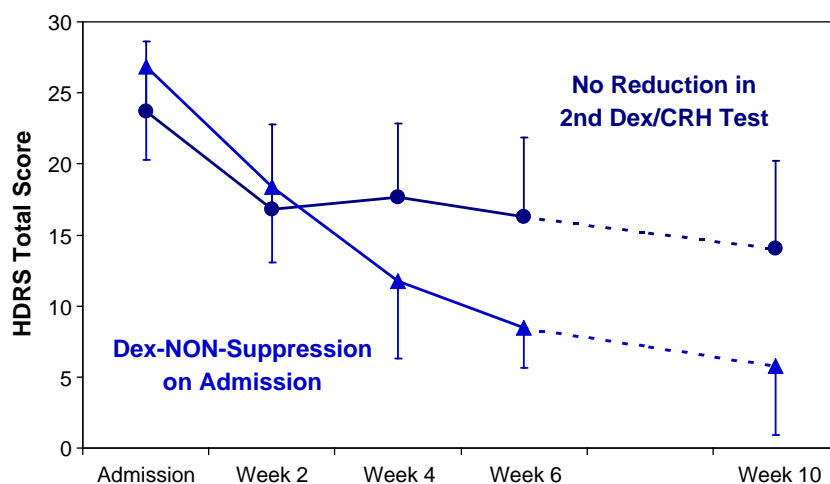


Fig. 3. Dex suppresser status on admission and change in cortisol response to a second dex/CRH test predicts psychopathological improvement (HDRS total scores, mean \pm S.D.) ($p < 0.001$). Favorable response prognosis was defined as dex non-suppression on admission indicating pronounced alteration of the HPA system which can be satisfactorily treated by antidepressants. Poor response prognosis was defined as failure to achieve a lower cortisol response to a second dex/CRH test about 2 to 3 weeks later indicating ineffectiveness of the current treatment to normalize corticosteroid receptor function.

6. Conclusion

There is compelling evidence that impaired corticosteroid receptor function is the key mechanism in the pathogenesis of depression resulting in a dysfunctional regulation of the hypothalamus–pituitary–adrenocortical (HPA) system, which can be most sensitively detected with the combined dexamethasone (dex)/corticotropin releasing hormone (CRH) test. Treatment with different kinds of antidepressants is associated with a normalization of the neuroendocrine response to the combined dex/CRH test suggesting normalization of impaired corticosteroid receptor signaling as the final common pathway of antidepressants with different pharmacodynamic profiles. This is in accordance with preclinical data showing that different types of antidepressants increase glucocorticoid receptor (GR) gene expression and enhance GR sensitivity. We presented data suggesting the suitability of the combined dex/CRH test as a surrogate marker for antidepressant drug efficacy. A new drug can be considered as clinically effective if its application in depressed patients with initially altered neuroendocrine response to the combined dex/CRH test leads to a normalization of the test indicating that treatment with the drug resolves impaired corticosteroid receptor signaling. Studies comparing the outcome of effective and ineffective compounds on the combined dex/CRH test are so far not available. However, the reported evidence suggests that the combined dex/CRH test can be applied as an effective screening tool to judge whether new compounds developed as antidepressants provide sufficient efficacy to normalize corticoid receptor signaling in depressed patients.

The high rate of depressed patients failing to respond to an initial antidepressant treatment strategy gives compelling reason to search for surrogate markers providing early information on improvement (response) or lack of improvement (non-response) in order to change an ineffective treatment strategy at the earliest possible time. The combined dex/CRH test appears most promising to serve as a surrogate marker for treatment response in depression, since an alteration of the HPA system during an acute episode and its normalization after successful treatment is the most consistently observed laboratory finding in depression.

In order to judge the suitability of the combined dex/CRH test to serve as a surrogate marker for treatment response, the relevant prerequisites have to be discussed. According to Fleming and DeMets (1996), a surrogate marker for treatment response should meet the following requirements: reflection of a major causal pathway of the disease process, capturing the net effect of treatment on the clinical outcome, and prediction of intervention effects on clinical outcome. We summarized own results and findings from the literature suggesting that these requirements are fulfilled. (1) Impaired corticosteroid receptor signaling and the regulatory effects of antidepressants on HPA alterations

are considered as key mechanisms in the pathogenesis of the disease process. These alterations are reflected by an elevated cortisol response to the combined dex/CRH test and by its normalization after successful antidepressant treatment. (2) At least in dexamethasone non-suppressors, the cortisol response to CRH captures the net effect of the antidepressant treatment on the clinical outcome to a considerable degree. (3) Change of the cortisol response to the combined dex/CRH test predicts the clinical outcome in terms of response and relapse. If a drug treatment fails to result in a normalization of the dex/CRH test, a change of the treatment strategy is recommended.

Taken together, the combined dex/CRH test can be considered as a promising candidate to serve as a surrogate marker for drug efficacy and treatment response in depression. Normalization of impaired corticosteroid receptor signaling seems to be the final common pathway of antidepressants from different drug classes. Consequently, a clinically effective antidepressant should be capable to normalize dysregulations of the HPA system in patients with initially elevated neuroendocrine response to the combined dex/CRH test. Furthermore, change in HPA system function anticipates the course of the disorder; therefore, the combined dex/CRH test serves as a valuable tool for predicting non-response at the earliest possible time and helps to avoid leaving patients under an inefficient medication and to save direct and indirect costs for the health care system.

Some limitations have to be mentioned. Although the plasma cortisol response to the test is relatively refractory to a variety of possible confounders (caffeine and nicotine consumption, acute stressors, weight, intake of benzodiazepines, and kind of antidepressant treatment) mood stabilizers like carbamazepine and lithium may obscure the test result. Furthermore, not all patients with depressive symptoms show a dysregulation of the HPA system. This is especially the case in chronic depression. In these patients the interpretation of a single test result is impeded, but change of neuroendocrine responses to consecutive tests, however, may be still of value. Further systematic studies including a large cross-cultural validation study are under way to confirm that the combined dex/CRH test is a suitable tool to serve as a surrogate marker in depression.

References

- Arana, G.W.B., Ornstein, M., 1985. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. *Arch. Gen. Psychiatry* 42, 1193–1204.
- Barden, N., 1996. Modulation of glucocorticoid receptor gene expression by antidepressant drugs. *Pharmacopsychiatry* 29, 12–22.
- Belanoff, J.K., Rothschild, A.J., Cassidy, F., DeBattista, C., Baulieu, E.-E., Schold, C., Schatzberg, A.F., 2002. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol. Psychiatry* 52, 386–392.
- Bschor, B., Adli, M., Baethge, C., Eichmann, U., Ising, M., Uhr, M., Modell, S., Künzel, H., Müller-Oerlinghausen, B., Bauer, M., 2002. Lithium augmentation increases the ACTH and cortisol response in the

- combined DEX/CRH test in unipolar major depression. *Neuropsychopharmacology* 27, 470–478.
- Bschor, B., Baethge, C., Adli, M., Eichmann, U., Ising, M., Uhr, M., Modell, S., Künzel, H., Müller-Oerlinghausen, B., Bauer, M., 2003. Association between response to lithium augmentation and the combined DEX/CRH test in major depressive disorder. *J. Psychiatr. Res.* 37, 135–143.
- Deuschle, M., Schmider, J., Weber, B., Standhardt, H., Korner, A., Lammers, C.H., Schweiger, U., Hartmann, A., Heuser, I., 1997. Pulse-dosing and conventional application of doxepin: effects on psychopathology and hypothalamus–pituitary–adrenal (HPA) system. *J. Clin. Psychopharmacol.* 17, 156–160.
- Deuschle, M., Schweiger, U., Gotthardt, U., Weber, B., Korner, A., Schmider, J., Standhardt, H., Lammers, C.H., Krumm, B., Heuser, I.J., 1998. The combined dexamethasone/corticotropin-releasing hormone stimulation test is more closely associated with features of diurnal activity of the hypothalamo–pituitary–adrenocortical system than the dexamethasone suppression test. *Biol. Psychiatry* 43, 762–766.
- Fleming, T.R., DeMets, D.L., 1996. Surrogate end points in clinical trials: are we being misled? *Ann. Intern. Med.* 125, 605–613.
- Frieboes, R.M., Sonntag, A., Yassouridis, A., Eap, C.B., Baumann, P., Steiger, A., 2003. Clinical outcome after trimipramine in patients with delusional depression—a pilot study. *Pharmacopsychiatry* 36, 12–17.
- Gitlin, M.J., Gerner, R.H., 1986. The dexamethasone suppression test and response to somatic treatment: a review. *J. Clin. Psychiatry* 47, 16–21.
- Grasser, A., Moller, A., Backmund, H., Yassouridis, A., Holsboer, F., 1996. Heterogeneity of hypothalamic–pituitary–adrenal system response to a combined dexamethasone–CRH test in multiple sclerosis. *Exp. Clin. Endocrinol. Diabetes* 104, 31–37.
- Greden, J.F., Gardner, R., King, D., Grunhaus, L., Carroll, B.J., Kronfol, Z., 1983. Dexamethasone suppression tests in antidepressant treatment of melancholia. The process of normalization and test–retest reproducibility. *Arch. Gen. Psychiatry* 40, 493–500.
- Hatzinger, M., Reul, J.M., Landgraf, R., Holsboer, F., Neumann, I., 1996. Combined dexamethasone/CRH test in rats: hypothalamo–pituitary–adrenocortical system alterations in aging. *Neuroendocrinology* 64, 349–356.
- Hatzinger, M., Wotjak, C.T., Naruo, T., Simchen, R., Keck, M.E., Landgraf, R., Holsboer, F., Neumann, I.D., 2000. Endogenous vasopressin contributes to hypothalamic–pituitary–adrenocortical alterations in aged rats. *J. Endocrinol.* 164, 197–205.
- Heuser, I.J., Yassouridis, A., Holsboer, F., 1994. The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *J. Psychiatr. Res.* 28, 341–356.
- Heuser, I.J., Schweiger, U., Gotthardt, U., Schmider, J., Lammers, C.H., Dettling, M., Yassouridis, A., Holsboer, F., 1996. Pituitary–adrenal–system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. *Am. J. Psychiatry* 153, 93–99.
- Holsboer, F., 1983. Prediction of clinical course by dexamethasone suppression test (DST) response in depressed patients—physiological and clinical construct validity of the DST. *Pharmacopsychiatry* 16, 186–191.
- Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23, 477–501.
- Holsboer, F., Barden, N., 1996. Antidepressants and hypothalamic–pituitary–adrenocortical regulation. *Endocr. Rev.* 17, 187–205.
- Holsboer, F., Liebl, R., Hofschuster, E., 1982. Repeated dexamethasone suppression test during depressive illness. Normalisation of test result compared with clinical improvement. *J. Affect. Disord.* 4, 93–101.
- Holsboer, F., von Bardeleben, U., Wiedemann, K., Müller, O.A., Stalla, G.K., 1987. Serial assessment of corticotropin-releasing hormone response after dexamethasone in depression. Implications for pathophysiology of DST nonsuppression. *Biol. Psychiatry* 22, 228–234.
- Holsboer-Trachsler, E., Stohler, R., Hatzinger, M., 1991. Repeated administration of the combined dexamethasone–human corticotropin releasing hormone stimulation test during treatment of depression. *Psychiatry Res.* 38, 163–171.
- Holsboer-Trachsler, E., Hemminger, U., Hatzinger, M., Seifritz, E., Gerhard, U., Hobi, V., 1994. Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment—neurobiological and psychometric assessment of course. *J. Psychiatr. Res.* 28, 381–399.
- Joyce, P.R., Paykel, E.S., 1989. Predictors of drug response in depression. *Arch. Gen. Psychiatry* 46, 89–99.
- Keck, M.E., Holsboer, F., 2001. Hyperactivity of CRH neuronal circuits as a target for therapeutic interventions in affective disorders. *Peptides* 22, 835–844.
- Keck, M.E., Wigger, A., Welt, T., Müller, M.B., Gesing, A., Reul, J.M., Holsboer, F., Landgraf, R., Neumann, I.D., 2002. Vasopressin mediates the response of the combined dexamethasone/CRH test in hyper-anxious rats: implications for pathogenesis of affective disorders. *Neuropsychopharmacology* 26, 94–105.
- Keck, M.E., Welt, T., Müller, M.B., Uhr, M., Ohl, F., Wigger, A., Toschi, N., Holsboer, F., Landgraf, R., 2003. Reduction of hypothalamic vasopressinergic hyperdrive contributes to clinically relevant behavioral and neuroendocrine effects of chronic paroxetine treatment in a psychopathological rat model. *Neuropsychopharmacology* 28, 235–243.
- Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., Kendler, K.S., 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch. Gen. Psychiatry* 51, 8–19.
- Kunugi, H., Urushibara, T., Nanko, S., 2004. Combined Dex/CRH test among Japanese patients with major depression. *J. Psychiatr. Res.* 38, 123–128.
- Künzel, H.E., Binder, E., Nickel, T., Ising, M., Fuchs, B., Majer, M., Pfennig, A., Ernst, G., Schmid, D.A., Uhr, M., Holsboer, F., Modell, S., 2003. Pharmacological and non-pharmacological factors influencing hypothalamic–pituitary–adrenocortical axis reactivity in acutely depressed psychiatric in-patients, measured by the Dex–CRH test. *Neuropsychopharmacology* 28, 2169–2178.
- Lammers, C.H., Garcia-Borreguero, D., Schmider, J., Gotthardt, U., Dettling, M., Holsboer, F., Heuser, I.J., 1995. Combined dexamethasone/corticotropin-releasing hormone test in patients with schizophrenia and in normal controls. *Biol. Psychiatry* 38, 803–807.
- Modell, S., Yassouridis, A., Huber, J., Holsboer, F., 1997. Corticosteroid receptor function is decreased in depressed patients. *Neuroendocrinology* 65, 216–222.
- Montkowski, A., Barden, N., Wotjak, C., Stec, I., Ganster, J., Meaney, M., Engelmann, M., Reul, J.M., Landgraf, R., Holsboer, F., 1995. Long-term antidepressant treatment reduces behavioural deficits in transgenic mice with impaired glucocorticoid receptor function. *J. Neuroendocrinol.* 7, 841–845.
- Nelson, J.C., 1998. Overcoming treatment resistance in depression. *J. Clin. Psychiatry* 59 (Suppl. 16), 13–19.
- Nickel, T., Sonntag, A., Schill, J., Zobel, A.W., Ackl, N., Brunner, A., Murck, H., Ising, M., Yassouridis, A., Steiger, A., Zihl, J., Holsboer, F., 2003. Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J. Clin. Psychopharmacol.* 28, 155–168.
- Nierenberg, A.A., 1994. The treatment of severe depression: is there an efficacy gap between SSRI and TCA antidepressant generations? *J. Clin. Psychiatry* 55 (Suppl. A), 55–59.
- Oshima, A., Yamashita, S., Owashi, T., Murata, T., Tadokoro, C., Miyaoka, H., Kamijima, K., Higuchi, T., 2000. The differential ACTH responses to combined dexamethasone/CRH administration in major depressive and dysthymic disorders. *J. Psychiatr. Res.* 34, 325–328.
- Pariante, C.M., Thomas, S.A., Lovestone, S., Makoff, A., Kerwin, R.W., 2004. Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology* 29, 423–447.
- Pepin, M.C., Pothier, F., Barden, N., 1992a. Antidepressant drug action in a transgenic mouse model of the endocrine changes seen in depression. *Mol. Pharmacol.* 42, 991–995.
- Pepin, M.C., Pothier, F., Barden, N., 1992b. Impaired type II glucocorticoid-receptor function in mice bearing antisense RNA transgene. *Nature* 355, 725–728.

- Quitkin, F.M., McGrath, P.J., Stewart, J.W., Ocepek-Welikson, K., Taylor, B.P., Nunes, E., Deliyannides, D., Agosti, V., Donovan, S.J., Petkova, E., Klein, D.F., 1996. Chronological milestones to guide drug change. When should clinicians switch antidepressants? *Arch. Gen. Psychiatry* 53, 785–792.
- Raison, C.L., Miller, A.H., 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am. J. Psychiatry* 160, 1554–1565.
- Ribeiro, S.C., Tandon, R., Grunhaus, L., Greden, J.F., 1993. The DST as a predictor of outcome in depression: a meta-analysis. *Am. J. Psychiatry* 150, 1618–1629.
- Rinne, T., de Kloet, E.R., Wouters, L., Goekoop, J.G., de Rijk, R.H., van den Brink, W., 2002. Hyperresponsiveness of hypothalamic–pituitary–adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. *Biol. Psychiatry* 52, 1102–1112.
- Rinne, T., de Kloet, E.R., Wouters, L., Goekoop, J.G., de Rijk, R.H., van den Brink, W., 2003. Fluvoxamine reduces responsiveness of HPA axis in adult female BPD patients with a history of sustained childhood abuse. *Neuropsychopharmacology* 28, 126–132.
- Rybakowski, J.K., Twardowska, K., 1999. The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. *J. Psychiatr. Res.* 33, 363–370.
- Schmider, J., Lammers, C.H., Gotthardt, U., Dettling, M., Holsboer, F., Heuser, I.J., 1995. Combined dexamethasone/corticotropin-releasing hormone test in acute and remitted manic patients, in acute depression, and in normal controls. I. *Biol. Psychiatry* 38, 797–802.
- Schreiber, W., Lauer, C.J., Krumrey, K., Holsboer, F., Krieg, J.C., 1996. Dysregulation of the hypothalamic–pituitary–adrenocortical system in panic disorder. *Neuropsychopharmacology* 15, 7–15.
- Schüle, C., Baghai, T., Zwanzger, P., Ella, R., Eser, D., Padberg, F., Möller, H.J., Rupprecht, R., 2003. Attenuation of hypothalamic–pituitary–adrenocortical hyperactivity in depressed patients by mirtazapine. *Psychopharmacology* 166, 271–275.
- Scott, L.V., Dinan, T.G., 2002. Vasopressin as a target for antidepressant development: an assessment of the available evidence. *J. Affect. Disord.* 72, 113–124.
- Simon, G.E., 2002. Evidence review: efficacy and effectiveness of antidepressant treatment in primary care. *Gen. Hosp. Psych.* 24, 213–224.
- Simon, G., Ormel, J., von Korff, M., Barlow, W., 1995. Health care costs associated with depressive and anxiety disorder in primary care. *Am. J. Psychiatry* 152, 352–357.
- Stec, I., Barden, N., Reul, J.M., Holsboer, F., 1994. Dexamethasone nonsuppression in transgenic mice expressing antisense RNA to the glucocorticoid receptor. *J. Psychiatr. Res.* 28, 1–5.
- Then-Bergh, F., Kümpfel, T., Trenkwalder, C., Rupprecht, R., Holsboer, F., 1999. Dysregulation of the hypothalamo–pituitary–adrenal axis is related to the clinical course of MS. *Neurology* 53, 772–777.
- Then-Bergh, F., Kümpfel, T., Grasser, A., Rupprecht, R., Holsboer, F., Trenkwalder, C., 2001. Combined treatment with corticosteroids and moclobemide favors normalization of hypothalamo–pituitary–adrenal axis dysregulation in relapsing–remitting multiple sclerosis: a randomized, double blind trial. *J. Clin. Endocrinol. Metab.* 86, 1610–1615.
- Thompson, D., Richardson, E., 1999. Current issues in the economics of depression management. *Curr. Psychiatry Rep.* 1, 125–134.
- von Bardeleben, U., Holsboer, F., 1989. Cortisol response to a combined dexamethasone–human corticotropin-releasing hormone challenge in patients with depression. *J. Neuroendocrinol.* 1, 485–488.
- von Bardeleben, U., Holsboer, F., 1991. Effect of age on the cortisol response to human corticotropin-releasing hormone in depressed patients pretreated with dexamethasone. *Biol. Psychiatry* 29, 1042–1050.
- von Bardeleben, U., Holsboer, F., Stalla, G.K., Müller, O.A., 1985. Combined administration of human corticotropin-releasing factor and lysine vasopressin induces cortisol escape from dexamethasone suppression in healthy subjects. *Life Sci.* 37, 1613–1618.
- von Bardeleben, U., Wiedemann, K., Stalla, G.K., Müller, O.A., Holsboer, F., 1988. Exaggerated corticotrophic cell response to human corticotropin-releasing hormone in two patients during long-term carbamazepine treatment. *Biol. Psychiatry* 24, 331–335.
- Watson, S., Gallagher, P., Del-Estal, D., Hearn, A., Ferrier, I.N., Young, A.H., 2002. Hypothalamic–pituitary–adrenal axis function in patients with chronic depression. *Psychol. Med.* 32, 1021–1028.
- Yanovski, J.A., Cutler, G.B., Chrousos, G.P., Nieman, L.K., 1993. Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration—a new test to distinguish Cushing's syndrome from pseudo Cushing's states. *JAMA* 269, 2232–2238.
- Yanovski, J.A., Cutler, G.B., Chrousos, G.P., Nieman, L.K., 1998. The dexamethasone-suppressed corticotropin-releasing hormone stimulation test differentiates mild Cushing's disease from normal physiology. *J. Clin. Endocrinol. Metab.* 83, 348–352.
- Zobel, A.W., Nickel, T., Sonntag, A., Uhr, M., Holsboer, F., Ising, M., 2001. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression: a prospective study. *J. Psychiatr. Res.* 35, 83–94.