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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 suppresser 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/CHR 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.

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

Contents

Abbreviations: ACTH, adrenocorticotropic 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).