



Chronic ACTH autoantibodies are a significant pathological factor in the disruption of the hypothalamic–pituitary–adrenal axis in chronic fatigue syndrome, anorexia nervosa and major depression

R. Wheatland

The Endocrine Research Project, 574 Sims Road, Santa Cruz, CA 95060, USA

Received 23 February 2005; accepted 24 February 2005

Summary Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is a commonly recognized feature of many pathological conditions. Abnormal adrenal responses to experimental manipulation have been well documented in patients suffering from chronic fatigue syndrome, anorexia nervosa and major depression. Yet no defect of any single organ, gland or brain region has been identified as a cause of these abnormalities. The disruption of the HPA axis that occurs in these conditions can be understood if an interfering factor is present in these patients. Evidence indicates that this interfering factor is adrenocorticotropin hormone (ACTH) autoantibodies. Chronic high levels of ACTH autoantibodies will significantly disrupt the HPA axis and force the body to compensate for an impaired cortisol response. The resulting effect of chronic ACTH autoantibody interference is the manifestation of adrenocortical insufficient symptoms and psychological disturbances. Some symptoms of chronic fatigue syndrome, anorexia nervosa and major depression, such as anxiety, are the adverse effects of mechanisms compensating for less effective ACTH due to autoantibodies. Furthermore, these patients engage in extraordinary behaviors, such as self-injury, to increase their cortisol levels. When this compensation is inadequate, symptoms of adrenocortical insufficiency appear. Corticosteroid supplements have been demonstrated to be an effective treatment for chronic fatigue syndrome, anorexia nervosa and major depression. It allows the patients to have the corticosteroids they require for daily functioning and daily stressors. This therapy will relieve the patients of their symptoms of adrenocortical insufficiency and permit their cortisol-stimulating mechanisms to operate at levels that will not cause pathological problems.
© 2005 Elsevier Ltd. All rights reserved.

Introduction

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is a commonly recognized

E-mail address: rwheatla@query.com.

Table 1 Characterization of the results of studies investigating the response of the hypothalamic–pituitary–adrenal axis in patients suffering from chronic fatigue syndrome, anorexia nervosa and major depression relative to the response from apparently healthy control subjects

	Chronic fatigue syndrome	Anorexia nervosa	Major depression
CSF CRH	Normal [1]	High [6,7]	High [13]
Basal serum cortisol	Low [1]	High [8]	High [14,15]
Net serum cortisol difference after CRH stimulation	Attenuated [1,2]	Attenuated [6,9]	Normal [16–18]
Serum cortisol after low-dose (1 µg) ACTH _{1–24} stimulation	Attenuated [3]	NA	NA
Serum cortisol after high-dose (250 µg) ACTH _{1–24} stimulation	Attenuated [1]	Attenuated [10]	Exaggerated [19]
Serum cortisol after insulin-induced hypoglycemia	Normal [4,5]	Normal [11,12]	Normal [20], Attenuated [21]

CSF, cerebrospinal fluid; CRH, corticotropin-releasing hormone; NA, not available.

feature of many pathological conditions. Abnormal adrenal responses to experimental manipulation have been well documented in patients suffering from chronic fatigue syndrome (CFS), anorexia nervosa (AN) and major depression (MD). Yet no defect of any single organ, gland or brain region has been identified as a cause of these abnormalities. The disruption of the HPA axis that occurs in these conditions can be understood if an interfering factor is present in these patients. Evidence indicates that this interfering factor is adrenocorticotropin hormone (ACTH) autoantibodies. Chronic high levels of ACTH autoantibodies will significantly disrupt the HPA axis and force the body to compensate for an impaired cortisol response. The resulting effect of chronic ACTH autoantibody interference is the manifestation of adrenocortical insufficient symptoms and psychological disturbances.

Table 1 lists some of the aberrant experimental results that are representative of the HPA dysregulation found in patients with CFS, AN and MD. Even though these results are not absolute, in that many patients do not respond as indicated and other studies report conflicting results, these results still convey that there are significant abnormalities in the HPA regulatory responses of these patients, compared to apparently healthy control subjects.

Since HPA dysregulation is a prominent feature of CFS, AN and MD, and the dysregulation diminishes as sufferers of these disorders recover, identification of the cause of the dysregulation should prove helpful in understanding the etiology of these disorders. In 2002, Fetissov et al. [22] presented evidence indicating that a significant percentage of sufferers of anorexia nervosa and/or bulimia nervosa have antibodies to ACTH in their sera. Interference by ACTH autoantibodies is a credible cause of the HPA dysregulation and symptoms observed in CFS, AN and MD. Furthermore, if ACTH autoantibodies are involved in the pathogenesis of these disorders, it explains why past studies were unable to localize a defect in the HPA axes of its sufferers (without interference, their HPA axes would function properly).

Behavioral/neuroendocrine compensation for ineffective ACTH and its adverse effects

Cortisol is a crucial hormone for maintaining well-being and homeostasis. ACTH secreted by the pituitary gland is a major governor of the production and secretion of cortisol by the adrenal glands. When antibodies interfere with ACTH, to ensure sufficient

cortisol levels, sufferers respond with various behavioral and neuroendocrine modifications that will hyperactivate primary and alternate neuroendocrine pathways for stimulating cortisol secretion. Unfortunately, chronic overactivation of these pathways is insufficient for long-term compensation and is accompanied by serious psychological side effects. Furthermore, the sufferer may discover that certain behaviors are beneficial for the short-term relief of adrenocortical insufficient symptoms. But, again, these behaviors become less effective with long-term utilization and are, ultimately, harmful. When this compensation is inadequate, cortisol levels will be less than what the body requires and adrenocortical insufficient symptoms will become apparent. These common symptoms among CFS, AN and MD patients are also common symptoms during adrenocortical insufficiency: fatigue, weakness, mental depression, anorexia, sleep disturbances, inability to concentrate, headaches, and muscle and back pain [23].

Several of the symptoms of CFS, AN and MD can be attributed to the extraordinary behavioral and neuroendocrine activity that is necessary to compensate for ineffective ACTH. For example, corticotropin-releasing hormone (CRH), secreted by the hypothalamus, stimulates the production and secretion of ACTH. As ACTH becomes less effective due to ACTH autoantibodies, CRH secretion will increase in an attempt to raise cortisol levels by stimulating more ACTH secretion. But the increased CRH level also affects other stress-related physiologic and cognitive processes. Intracerebroventricular administration of CRH in rats increased behaviors associated with an anxiogenic effect [24,25]. Whereas administration of a CRH receptor antagonist attenuated behavioral, neuroendocrine and autonomic responses to stress in primates [26]. Therefore, as a result of interfering ACTH autoantibodies, high levels of CRH can account for the anxiety felt by patients with CFS, AN and MD.

It is reasonable that high CRH levels should invoke anxiety. If humans were to encounter painless stressors and not feel anxious, they would be less motivated to do something to stop or avoid the stressor, allowing the stressor to cause harm later. But chronically high CRH levels due to chronic ACTH autoantibodies invoke chronic anxiety. There is little the sufferer can do to alter their situation to lower their anxiety level. Therefore, they feel trapped in an inescapable stressful situation, because they are. This can lead to an apathetic mood as a method for coping. If anxiety cannot be relieved, it may be best to ignore anything stress-related. As the anxiety worsens, this apathy for stressors may spread to all activities, that is,

becoming despair. A state of apathy or despair has also been observed in animals subjected to inescapable stressors [27].

Some CFS patients are characterized by profound physical inactivity [28]. By resting and avoiding overexertion, these patients are able to conserve their limited supply of cortisol. When they do need to be active, they require lengthy and excessive rest periods afterwards to restore their cortisol to adequate levels. Avoiding other stressful situations, such as social stress, would explain the social isolation of CFS.

Sufferers of AN engage in three compensatory behaviors that can raise their cortisol levels: severe dieting, excessive exercise and self-injury. Blood cortisol levels will rise in response to severe food restriction due to increased secretion of cortisol, increased cortisol half-life and a decrease in cortisol's metabolic clearance rate, as demonstrated in studies of healthy, fasting women and subjects with protein-calorie malnutrition. In addition, high CRH levels may play a significant role in the food restriction of AN due to CRH's well-documented anorexigenic effect [29,30]. Perhaps high CRH levels induce anorexia to engage an alternate mechanism for raising cortisol levels.

Self-injury may seem to be an irrational act, but it is actually an effective non-ACTH-mediated method for increasing cortisol levels. Güllner et al. [31] measured ACTH and cortisol levels following experimentally induced pain in normal subjects. They found that, after 5 and 10 min of pain and 30 min after the discontinuation of pain, cortisol levels were significantly increased but ACTH levels were not affected. They concluded, "Cortisol secretion by the adrenal cortex may have been stimulated directly by some other agent, possibly mediated by efferent nerve impulses, suggesting a possible regulation of cortisol secretion by a factor other than ACTH, at least under conditions of stress." It has been demonstrated that cortisol secretion can be regulated by adrenal innervation [32]. Therefore, if some AN sufferers have a limited ability to stimulate cortisol secretion using their normal ACTH mechanism, they may be using the stress of self-injury as an alternate mechanism for stimulating cortisol secretion. Furthermore, it is possible that suicidal ideation is a form of self-injury, psychogenic self-injury.

The interference of ACTH autoantibodies with the dynamic cortisol response to stressors explains the stress-related aspects of CFS, AN and MD. Not only do sufferers demonstrate an abnormal reaction to stressors, but increased stress pressures the compensating cortisol-stimulating mechanisms to increased overactivity, thus increasing their adverse effects. Furthermore, the significant placebo

effect observed in treatment studies of CFS, AN and MD is understandable. Stress reduction would seem to be the primary effect of a placebo. Stress reduction will lessen the body's cortisol requirement, which will relieve the pressure for behavioral and neuroendocrine compensation for ineffective ACTH and thus diminish their associated adverse effects (symptoms).

Although chronic ACTH autoantibodies are a common pathological factor in CFS, AN and MD, these syndromes are differentiated on the basis of the differences in their symptom profiles, which are a reflection of the set of compensatory mechanisms that the patient is using to increase their cortisol levels.

Corticosteroid treatment effectiveness

If CFS, AN and MD patients suffer from an abnormal cortisol response due to interfering ACTH autoantibodies, then administration of subphysiologic doses of corticosteroids should prove an effective treatment for relieving their symptoms. For CFS, two randomized controlled trials have reported symptomatic improvement in association with low-dose hydrocortisone supplementation [33,34]. It is likely that an even better clinical response will be seen if superior corticosteroid supplement treatment regimens are utilized (see below).

In a previous paper, I reviewed the successful treatment of AN using subphysiologic doses of corticosteroids or non-human ACTH [35]. Low-dose corticosteroid supplements were effective, high-dose corticosteroid supplements were ineffective. An additional case study has reported the effectiveness of treating AN with porcine ACTH: The prolonged treatment with corticotropin has allowed to appreciate results that would be discouraging if they were not clearly superior to the ones reached previously with all other established treatments (translation) [36]. Porcine ACTH is effective in the presence of autoantibodies to human ACTH because porcine ACTH is immunologically different from human ACTH and the ACTH autoantibodies have little, if any, affinity for it.

Table 2 lists the results of studies that treated depressed patients with non-human ACTH or corticosteroids. Many patients showed a good clinical response, including a persistent response for some after treatment had been discontinued. For some patients, it is possible that once their need for hypothalamic hyperactivity has been relieved for a short period, the hyperactivity will not return unless a significant stressor is encountered.

Discussion

This paper has described how chronic ACTH autoantibodies are a satisfying explanation for the symptoms and HPA dysregulation of CFS, AN and MD. The question remains as to why these patients have ACTH autoantibodies. Chronic ACTH autoantibodies are probably induced by a past or persistent infection [48]. Utilizing molecular mimicry of ACTH, infectious agents induce antibodies that crossreact with the host's ACTH. The infectious etiology of CFS, AN and MD may be apparent from the fact that three common symptoms of influenza-like infections are fatigue, anorexia and depression.

It appears that the body is well prepared with mechanisms for stimulating cortisol secretion in the presence of ACTH autoantibodies. For example, is ACTH secreted in pulses in an attempt to overwhelm ACTH autoantibody interference? By secreting ACTH faster than ACTH autoantibodies can be produced, can ACTH be effective for short periods before being neutralized by antibodies?

The endocrine and immune systems are naturally interrelated. But the production of ACTH autoantibodies creates a pathological interaction between these systems. When the endocrine system attempts to increase cortisol levels by secreting more ACTH, the immune system will counter this by producing additional ACTH autoantibodies. It is unlikely that the result of this competition will be an appropriate cortisol level. If the endocrine system is more successful, cortisol levels will probably end up high. If the immune system is more successful, the result will probably be insufficient cortisol levels. This imbalance may even demonstrate a daily fluctuation due to the circadian rhythms of the underlying processes. In addition, if the ACTH autoantibodies are induced by a persistent infection, the infection may affect the balance by becoming more or less active, depending on the current suitability of the host for the infection's prosperity.

The impact of interfering ACTH autoantibodies is important to the interpretation of two conventional assessments of HPA function: ACTH assays and the ACTH stimulation test. Numerous studies have measured serum ACTH levels in CFS, AN and MD patients, but none of the assays utilized were designed to measure ACTH levels in the presence of ACTH autoantibodies. Therefore, these ACTH measurements were not reliable, which would explain the frequent finding of paradoxical results and inconsistencies between studies. A more accurate analysis of ACTH levels can be attained by first acidifying the sample, then extracting the ACTH before measuring its concentration [49]. In

Table 2 Results of studies of depressed patients that utilized non-human ACTH or corticosteroids in their treatment

Cleghorn et al. (1950) [37] $N = 8$

Treatment: non-human ACTH –16 mg 6 times/day the first few days, then somewhat less on subsequent days (total dose ~500–700 mg over 7 days)

“Some showed a mild to moderate degree of improvement, which first set in 24 to 36 hours after commencing administration of ACTH. This usually took the form of increased freedom of movement, and greater interest in the surroundings; this then passed on to a slow subsiding of the delusional ideas, where these had been present. There was some increase in activity and participation, the patients beginning to show an ability to concentrate which allowed a few of them to read and to play cards. Smiling usually appeared about the second or third day. Some showed an improvement in sleep. There was a rapid increase in weight related to water retention, although there was also some gain in appetite. The last index to shift was usually the patient’s own report, for most of them remained unwilling to describe themselves as improved despite the fact that such improvement was discernible to some observers.

“When the drug was stopped, any improvement noted regressed in much the same course and at much the same speed, the patient beginning to show signs of fading out of the more cheerful mood about 24 hours after cessation of the drug administration and disappearing entirely by the end of the third or fourth day.”

Glaser et al. (1951) [38] $N = 1$

Treatment: cortisone 4050 mg over 29 days

“...eczematous child was a congenital deaf mute fourteen years; of age with severe, generalized, chronic, atopic dermatitis which in recent months had been accompanied by severe mental depression. She was hospitalized for cortisone therapy and cleared nicely over a period of twenty-nine days. ... With the clearing of the skin the mental depression disappeared. She remained well three weeks at home without hormone therapy, following which her skin and mental condition rapidly reverted to the same state as before hospitalization.”

Kurland (1965) [39] $N = 12$

Treatment: prednisone 15 mg daily for 1 to 2 weeks, then the dosage was tapered off progressively for a month

“The subjects in this study had histories of severe depressive reactions of over 3 months’ duration, were potentially suicidal, and had failed to respond previously to other antidepressive medications.”

“Most neurotic- and manic-depressive subjects became somewhat euphoric when continued on a dosage of prednisone which produced complete remission of depressive symptoms. The prednisone treatment appeared to relieve only the specific components of affect disorder.”

“During this study, reappearance of severe depressions occurred in 1 manic-depressive and 2 neurotic-depressives, in each case about 2 months after the discontinuation of the medication.”

McClure and Cleghorn (1969) [40] $N = 17$

Treatment: dexamethasone 0.75 mg at midnight for 4 weeks ($N = 2$), 3 weeks ($N = 1$), 2 weeks ($N = 14$). Antidepressant treatment then added (usually after 1 week)

“So far, all patients have responded favourably. During the second week of the treatment plan[,] when the combined therapy starts[,] there is a marked improvement in the mood of the patient. All patients have been discharged within four weeks from the hospital clinically recovered. ... The response is much swifter than that using imipramine alone. It would appear that the dexamethasone is a primer for imipramine in some way.”

Arana and Forbes (1991) [41] $N = 16$

Treatment: dexamethasone 4 mg i.v. bolus ($N = 16$) and additional 4 mg p.o. ($N = 7$) or i.v. ($N = 4$) between days 5 and 7

“Overall, 75% (12/16) showed a greater than 50% improvement in depressive symptomatology in a 10-day period and 4 patients. ... showed responses ranging between 16% to 30% improvement in HAM-D scores.”

Goodwin et al. (1992) [42] $N = 14$

Treatment: cortisol two i.v. boluses of 7 mg/kg separated by 6 hours (total ~1000 mg)

(continued on next page)

Table 2 (continued)

“...several patients showed clinically obvious mood elevation on the day following cortisol; this was not clinically sustained for more than 24 h.”

“...there was a significant difference in response between patient and control group for ratings of 'Good mood'; the mood of the patients significantly improved.”

“The subjective effects of cortisol infusion were striking and were the opposite of our expectations. Some patients showed an obvious clinical improvement which was most unexpected and was not sustained.”

Arana et al. (1995) [43] *N* = 19

Treatment: dexamethasone 4 mg daily for 4 days

“Seven (37%) of the 19 patients in the dexamethasone group, compared with one (6%) of the 18 patients in the placebo group, responded with a $\geq 50\%$ reduction in Hamilton depression scale score or a score of ≤ 14 .”

Dinan et al. (1997) [44] *N* = 10

Treatment: dexamethasone 3 mg daily for 4 days (augmentation to regular antidepressant therapy)

“Six patients showed a significant improvement, whilst two showed a minimal response. A good clinical response was associated with a high baseline cortisol level.”

“The observation that the responses persisted for 16 days after dexamethasone treatment was discontinued is of particular interest.”

Bodani et al. (1999) [45] *N* = 2

Treatment: dexamethasone 3 mg daily for 4 days (augmentation to regular antidepressant therapy)

Two elderly patients with resistant depression: “Both patients appeared to experience a modest but significant benefit from dexamethasone treatment.”

“Subsequent experience has shown that both patients have been able to live at home with moderate depressive symptoms and a much higher level of functioning than was present before treatment.”

DeBattista et al. (2000) [46] *N* = 6

Treatment: hydrocortisone 15 mg infusion over 2 hrs

“Patients who received hydrocortisone showed a mean decrease in Hamilton depression scale score of 8.4 (representing a 37% reduction) from day 1 to day 2, compared with a mean decrease of 1.2 points in the ovine CRH group and 1.3 points in the placebo group. ... Post hoc tests indicated that the hydrocortisone group improved significantly more than both the ovine CRH ($p < 0.05$) and placebo ($p < 0.01$) groups.”

“Intravenous administration of a moderate dose of hydrocortisone appears to produce robust and rapid improvement in Hamilton depression scale scores.”

“A review of symptom change scores revealed that ovine CRH and cortisol both improve core endogenous depressive symptoms (Core Endogenomorphic Scale) but that ovine CRH was associated with an increase in anxiety.”

Bouwer et al. (2000) [47] *N* = 6

Treatment: prednisone 7.5 mg daily for 4 weeks (augmentation to regular antidepressant therapy)

“Four of six patients treated showed a definite improvement in depression with a 50% or greater fall in HAM-D score. Two showed partial improvement. ... The response became apparent after 16 days of treatment.”

interpreting the results of the ACTH stimulation test, since the ACTH used is the least antigenic section of whole ACTH (the first 24 amino acids), it is unlikely that ACTH autoantibodies interfere with this test. But this test will only confirm that the adrenal glands can respond appropriately to an unnatural ACTH stimulus. If an adequate cortisol increase is observed in patients with symptoms of

adrenocortical insufficiency, it cannot be implied that pituitary ACTH secretion is inadequate.

ACTH and β -endorphin are derived from a common precursor molecule, pro-opiomelanocortin. In healthy subjects, in response to stimulation by CRH, ACTH and β -endorphin are secreted in parallel in equimolar concentrations [50]. If ACTH autoantibodies interfere with the immunoassay of

ACTH, it would explain why CRH stimulation in depressed patients provokes β -endorphin secretion similar to normal subjects but an apparently blunted ACTH response [18].

Due to their symptom overlap with CFS, AN and MD and evidence of HPA dysregulation, many other conditions are also likely to involve chronic ACTH autoantibodies in their pathogenesis, especially fibromyalgia, panic disorder, posttraumatic stress disorder, seasonal affective disorder and dysthymia. Chronic ACTH autoantibodies may even be responsible for the HPA dysregulation observed in many autoimmune diseases.

Another syndrome that is very likely to be due to chronic ACTH autoantibodies is isolated ACTH deficiency [51]. This syndrome is characterized by symptoms of adrenocortical insufficiency, low cortisol levels, a normal cortisol response to exogenous ACTH stimulation, no apparent pituitary dysfunction and low serum ACTH levels without low levels of other pituitary hormones. Many published cases of isolated ACTH deficiency received tentative diagnoses of AN because of the clinical similarity. The final diagnosis of isolated ACTH deficiency has generally been based on the result of a flawed ACTH radioimmunoassay or indirect tests of ACTH levels. It is unlikely that isolated ACTH deficiency is a specific disorder. Most cases may be better characterized as adrenocortical insufficiency due to chronic ACTH autoantibodies.

Corticosteroid supplement treatment regimens

The goal of corticosteroid supplement therapy is to supply the corticosteroid that is not being produced endogenously while attempting to mimic the natural cortisol rhythm. Administering hydrocortisone once a day for corticosteroid supplementation is generally inadequate because the half-life of hydrocortisone is about 2 h. By assessing well-being scores in adrenocortical insufficient patients being treated with hydrocortisone, Groves et al. [52] suggest that a thrice daily regimen is superior to a twice daily regimen for obtaining a more constant plasma cortisol level and avoiding a deterioration of well-being in the mid-afternoon. Dr. Jefferies [53] recommends taking hydrocortisone four times daily in decreasing dosages to more closely imitate the diurnal rhythm and produce more energy and less fatigue. Some patients may prefer the convenience of taking a cortisol analogue, such as prednisone, which needs to be administered only

twice a day due to its longer half-life. While the use of cortisol analogues will prolong the rise in the patient's corticosteroid level, they are less likely to be able to mimic the natural cortisol rhythm.

Conclusions

Significant levels of chronic ACTH autoantibodies are a common pathological factor in CFS, AN and MD. These antibodies interfere with ACTH's ability to stimulate the production and secretion of cortisol, causing HPA dysregulation. As a result, patients suffer from the symptoms of adrenocortical insufficiency and the side effects of overactive cortisol-stimulating mechanisms utilized to compensate for this interference.

Corticosteroid supplement therapy is an appropriate treatment for CFS, AN and MD. It allows the patients to have the corticosteroids they require for daily functioning and daily stressors. This therapy will relieve the patients of their symptoms of adrenocortical insufficiency and permit their cortisol-stimulating mechanisms to operate at levels that will not cause pathological problems.

References

- [1] Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, et al. Evidence for impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 1991;73(6):1224–34.
- [2] Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. *Acta Psychiatr Scand* 1998;97(6):450–7.
- [3] Scott LV, Medbak S, Dinan TG. The low dose ACTH test in chronic fatigue syndrome and in health. *Clin Endocrinol (Oxf)* 1998;48(6):733–7.
- [4] Gaab J, Hüster D, Peisen R, Engert V, Heitz V, Schad T, et al. Hypothalamic–pituitary–adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. *Psychosom Med* 2002;64(6):951–62.
- [5] Bearn J, Allain T, Coskeran P, Munro N, Butler J, McGregor A, et al. Neuroendocrine responses to d-fenfluramine and insulin-induced hypoglycemia in chronic fatigue syndrome. *Biol Psychiatry* 1995;37(4):245–52.
- [6] Hotta M, Shibasaki T, Masuda A, Imaki T, Demura H, Ling N, et al. The responses of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. *J Clin Endocrinol Metab* 1986;62(2):319–24.
- [7] Kaye WH, Gwirtsman HE, George DT, Ebert MH, Jimerson DC, Tomai TP, et al. Elevated cerebrospinal fluid levels of immunoreactive corticotropin-releasing hormone in anorexia nervosa: relation to state of nutrition, adrenal function, and intensity of depression. *J Clin Endocrinol Metab* 1987;64(2):203–8.

- [8] Ferrari E, Fraschini F, Brambilla F. Hormonal circadian rhythms in eating disorders. *Biol Psychiatry* 1990;27(9):1007–20.
- [9] Gold PW, Gwirtsman H, Avgerinos PC, Nieman LK, Gallucci WT, Kaye W, et al. Abnormal hypothalamic–pituitary–adrenal function in anorexia nervosa. Pathophysiologic mechanisms in underweight and weight-corrected patients. *N Engl J Med* 1986;314(21):1335–42.
- [10] Takahara J, Hosogi H, Yunoki S, Hashimoto K, Uneki T, Ofuji T. Hypothalamic pituitary adrenal function in patients with anorexia nervosa. *Endocrinol Jpn* 1976;23(6):451–6.
- [11] Vigersky RA, Loriaux DL, Andersen AE, Lipsett MB. Anorexia nervosa: behavioural and hypothalamic aspects. *Clin Endocrinol Metab* 1976;5(2):517–35.
- [12] Nakagawa K, Matsubara M, Obara T, Kubo M, Akiyama K. Responses of pituitary and adrenal medulla to insulin-induced hypoglycemia in patients with anorexia nervosa. *Endocrinol Jpn* 1985;32(5):719–24.
- [13] Banki CM, Bissette G, Arato M, O'Connor L, Nemeroff CB. CSF corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. *Am J Psychiatry* 1987;144(7):873–7.
- [14] Mortola JF, Liu JH, Gillin JC, Rasmussen DD, Yen SS. Pulsatile rhythms of adrenocorticotropin (ACTH) and cortisol in women with endogenous depression: evidence for increased ACTH pulse frequency. *J Clin Endocrinol Metab* 1987;65(5):962–8.
- [15] Deuschle M, Schweiger U, Weber B, Gotthardt U, Körner A, Schmäder J, et al. Diurnal activity and pulsatility of the hypothalamus–pituitary–adrenal system in male depressed patients and healthy controls. *J Clin Endocrinol Metab* 1997;82(1):234–8.
- [16] Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH, et al. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *N Engl J Med* 1986;314(21):1329–35.
- [17] Holsboer F, von Bardeleben U, Buller R, Heuser I, Steiger A. Stimulation response to corticotropin-releasing hormone (CRH) in patients with depression, alcoholism and panic disorder. *Horm Metab Res Suppl* 1987;16:80–8.
- [18] Rupprecht R, Lesch KP, Müller U, Beck G, Beckmann H, Schulte HM. Blunted adrenocorticotropin but normal β -endorphin release after human corticotropin-releasing hormone administration in depression. *J Clin Endocrinol Metab* 1989;69(3):600–3.
- [19] Amsterdam JD, Winokur A, Abelman E, Lucki I, Rickels K. Cosyntropin (ACTH α_{1-24}) stimulation test in depressed patients and healthy subjects. *Am J Psychiatry* 1983;140(7):907–9.
- [20] Lopez JF, Kathol RG, Jaeckle RS, Meller W. The HPA axis response to insulin hypoglycemia in depression. *Biol Psychiatry* 1987;22(2):153–66.
- [21] Kathol RG, Gehris TL, Carroll BT, Samuelson SD, Pitts AF, Meller WH, et al. Blunted ACTH response to hypoglycemic stress in depressed patients but not in patients with schizophrenia. *J Psychiatr Res* 1992;26(2):103–16.
- [22] Fetissov SO, Hallman J, Oreland L, af Klinteberg B, Grenbäck E, Hulting AL, et al. Autoantibodies against α -MSH, ACTH, and LHRH in anorexia and bulimia nervosa patients. *Proc Natl Acad Sci USA* 2002;99(26):17155–60.
- [23] Tintera JW. The hypoadrenocortical state and its management. *NY State J Med* 1955;55(13):1869–76.
- [24] Dunn AJ, File SE. Corticotropin-releasing factor has an anxiogenic action in the social interaction test. *Horm Behav* 1987;21(2):193–202.
- [25] Butler PD, Weiss JM, Stout JC, Nemeroff CB. Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. *J Neurosci* 1990;10(1):176–83.
- [26] Habib KE, Weld KP, Rice KC, Pushkas J, Champoux M, Listwak S, et al. Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc Natl Acad Sci USA* 2000;97(11):6079–84.
- [27] Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature* 1977;266(5604):730–2.
- [28] van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *J Psychosom Res* 2000;49(5):373–9.
- [29] Morley JE, Levine AS. Corticotrophin releasing factor, grooming and ingestive behavior. *Life Sci* 1982;31(14):1459–64.
- [30] Glowa JR, Gold PW. Corticotropin releasing hormone produces profound anorexigenic effects in the rhesus monkey. *Neuropeptides* 1991;18(1):55–61.
- [31] Güllner HG, Nicholson WE, Wilson MG, Bartter FC, Orth DN. The response of plasma immunoreactive adrenocorticotropin, β -endorphin/ β -lipotropin, γ -lipotropin and cortisol to experimentally induced pain in normal subjects. *Clin Sci (Lond)* 1982;63(4):397–400.
- [32] Ottenweller JE, Meier AH. Adrenal innervation may be an extrapituitary mechanism able to regulate adrenocortical rhythmicity in rats. *Endocrinology* 1982;111(4):1334–8.
- [33] McKenzie R, O'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. *JAMA* 1998;280(12):1061–6.
- [34] Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. *Lancet* 1999;353(9151):455–8.
- [35] Wheatland R. Alternative treatment considerations in anorexia nervosa. *Med Hypotheses* 2002;59(6):710–5.
- [36] Reforzo Membrives J. Tratamiento de la anorexia mental con corticotrofina [Treatment of anorexia nervosa with corticotropin]. *Prensa Med Argent* 1951;38(52):3407–11.
- [37] Cleghorn RA, Graham BF, Saffran M, Cameron DE. A study of the effect of the pituitary ACTH in depressed patients. *Can Med Assoc J* 1950;63(4):329–31.
- [38] Glaser J, Siegel SC, Goldstein JD, Meltzer RS. Experiences with ACTH and cortisone in the treatment of asthma and eczema in infancy and childhood. *Ann Allergy* 1951;9(3):292–8.
- [39] Kurland HD. Physiologic treatment of depressive reactions: a pilot study. *Am J Psychiatry* 1965;122(4):457–8.
- [40] McClure DJ, Cleghorn RA. Hormone imbalance in depressive states. In: Bogoch S, editor. *The future of the brain sciences*. New York: Plenum Press; 1969. p. 525–53.
- [41] Arana GW, Forbes RA. Dexamethasone for the treatment of depression: a preliminary report. *J Clin Psychiatry* 1991;52(7):304–6.
- [42] Goodwin GM, Muir WJ, Seckl JR, Bennie J, Carroll S, Dick H, et al. The effects of cortisol infusion upon hormone secretion from the anterior pituitary and subjective mood in depressive illness and in controls. *J Affect Disord* 1992;26(2):73–83.
- [43] Arana GW, Santos AB, Laraia MT, McLeod-Bryant S, Beale MD, Rames LJ, et al. Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. *Am J Psychiatry* 1995;152(2):265–7.

- [44] Dinan TG, Lavelle E, Cooney J, Burnett F, Scott L, Dash A, et al. Dexamethasone augmentation in treatment-resistant depression. *Acta Psychiatr Scand* 1997;95(1):58–61.
- [45] Bodani M, Sheehan B, Philpot M. The use of dexamethasone in elderly patients with antidepressant-resistant depressive illness. *J Psychopharmacol* 1999;13(2):196–7.
- [46] DeBattista C, Posener JA, Kalehzan BM, Schatzberg AF. Acute antidepressant effects of intravenous hydrocortisone and CRH in depressed patients: a double-blind, placebo-controlled study. *Am J Psychiatry* 2000;157(8): 1334–1337.
- [47] Bouwer C, Claassen J, Dinan TG, Nemeroff CB. Prednisone augmentation in treatment-resistant depression with fatigue and hypocortisolemia: a case series. *Depress Anxiety* 2000;12(1):44–50.
- [48] Wheatland R. Molecular mimicry of ACTH in SARS – implications for corticosteroid treatment and prophylaxis. *Med Hypotheses* 2004;63(5):855–62.
- [49] Pranzatelli MR, Kao PC, Tate ED, Chaves E, Chez M, Dobyns WB, et al. Antibodies to ACTH in opsoclonus-myoclonus. *Neuropediatrics* 1993;24(3):131–3.
- [50] Jackson RV, DeCherney GS, DeBold CR, Sheldon WR, Alexander AN, Rivier J, et al. Synthetic ovine corticotropin-releasing hormone: simultaneous release of proopiomelanocortin peptides in man. *J Clin Endocrinol Metab* 1984;58(4):740–3.
- [51] Stacpoole PW, Interlandi JW, Nicholson WE, Rabin D. Isolated ACTH deficiency: a heterogeneous disorder. Critical review and report of four new cases. *Medicine (Baltimore)* 1982;61(1):13–24.
- [52] Groves RW, Toms GC, Houghton BJ, Monson JP. Corticosteroid replacement therapy: twice or thrice daily? *J R Soc Med* 1988;81(9):514–6.
- [53] Jefferies WM. *Safe uses of cortisol*. 2nd ed.. Springfield (IL): Charles C. Thomas; 1996.

Available online at www.sciencedirect.com

