Release of corticotropin after administration of corticotropin-releasing hormone in depressed patients in relation to the dexamethasone suppression test

Thalén B-E, Kjellman BF, Ljunggren JG, Akner G, Kågedal B, Wahlund B, Wetterberg L. Release of corticotropin after administration of corticotropin-releasing hormone in depressed patients in relation to the dexamethasone suppression test.
Acta Psychiatr Scand 1993: 87: 133–140. © Munksgaard 1993.

The possible hypersecretion involvement of corticotropin-releasing hormone (CRH) in the pathophysiology of hypothalamic-pituitary-adrenocortical axis disturbances in patients with major depressive episode and with an abnormal dexamethasone suppression test (DST) was investigated. The corticotropin (ACTH) and cortisol response to the injection of 45 μg of synthetic human CRH at 1630 were analyzed in 24 inpatients with normal (suppressors) or abnormal (nonsuppressors) DST. The outcome of the DST was analyzed using 3 cut-off points for the cortisol levels. The clinical assessments included two rating scales. The results showed that nonsuppressors had a significantly lower ACTH response to CRH stimulation than suppressors at all cut-off points (calculated as net area under the curve and as the difference between the peak and the baseline level) despite no significant differences in the severity of depression.

B.-E. Thalén [1], B. F. Kjellman [1], J.-G. Ljunggren [2], G. Akner [3], B. Kågedal [4], B. Wahlund [1], L. Wetterberg [1]

Departments of [1] Psychiatry and [2] Medicine, St. Göran's Hospital, [3] Department of Medical Nutrition, Huddinge University Hospital, Karolinska Institute, Stockholm, [4] Department of Clinical Chemistry, University Hospital, Linköping, Sweden

Key words: depression; dexamethasone suppression test; corticotropin-releasing hormone; ACTH; cortisol

Lennart Wetterberg, Karolinska Institute, Department of Psychiatry, St. Göran's Hospital, S-112 81 Stockholm, Sweden

Accepted for publication October 30, 1992

About 40–50% of the patients with major depressive disorder show disturbances in the hypothalamic-pituitary-adrenocortical (HPA) axis as expressed by plasma ACTH (1–4), cortisol (5–8), urinary free cortisol excretion (9, 10) inadequate suppressibility of cortisol by oral dexamethasone administration (9, 11), increased cerebrospinal fluid cortisol concentration (12) or a hyperresponsiveness of the adrenal cortex to exogenous ACTH (13–15).

The pathophysiological mechanism(s) behind the disturbance(s) remain unclear. The disturbances may involve corticotropin-releasing hormone (CRH) hypersecretion. This statement was based on studies on plasma ACTH and cortisol after the administration of CRH (16, 17) or other ACTH stimulatory factors (18), and on estimation of the CRH levels in the CSF (19–23) and CRH receptor-binding sites in the central nervous system (24).

During the last decade, we have done broad neuroendocrine testing on patients with affective disorders of different types and different severities (25–27). The laboratory results were correlated with the clinical history and disease symptoms and compared with those from healthy subjects. Regarding the HPA axis, the results confirmed that about 50% of the patients had abnormal responses to the dexamethasone suppression test (DST) in the acute depressive state. Most patients showed normal response in remission. The results showed that the disturbances in the HPA axis may involve CRH hypersecretion. We also found that the disturbances in the hypothalamic-pituitary-thyroid axis may involve a hypersecretion of thyrotropin-releasing hormone (27). No disturbances in the hypothalamic-pituitary-gonadal axis were found (28). The initial group of patients has been followed for 10 years or more; the long-term follow-up evaluation is in progress.

This study's goal was to further explain the possible involvement of a CRH hypersecretion behind the disturbances in the HPA axis. This study compared patients who have major depressive disorders and normal DST (suppressors) with patients who have abnormal DST (nonsuppressors). Their ACTH and cortisol responses were compared after they received human CRH. Previous studies (including ours) have compared the results from patients with results from healthy controls. The comparison between the 2 patient groups may increase the possibility to reveal differences, because about half of the patients have an apparently normal function of the

pressors when divided by the 3 different cut-off points in either of the two rating scales. CPRS mean ratings, when suppressors were compared with non-suppressors were: (1) 26.9 ± 1.2 *vs* 27.7 ± 1.2 – low cut-off point, (2) 27.8 ± 1.3 *vs* 26.4 ± 1.6 – medium cut-off point, (3) 27.8 ± 1.2 *vs* 26.1 ± 1.8 – high cut-off point. The corresponding values of the HRSD ratings were 25.0 ± 1.7 *vs* 27.4 ± 1.6; 26.0 ± 1.4 *vs* 26.4 ± 2.4 and 26.6 ± 1.3 *vs* 26.1 ± 2.7. Age, weight and medication did not covary with baseline levels or response levels of the hormones studied, neither in the whole sample nor in the subgroups.

Discussion

These results demonstrate that the nonsuppressors have significantly lower ACTH and cortisol responses to CRH stimulation than the suppressors – despite no significant differences in the total rating scores of their symptoms. Similar results were found regardless of the 3 different cut-off points that were used for evaluating the outcome of the DST.

The outcome of the DST depends on several factors. Many investigators have demonstrated that the specificity and sensitivity of the DST is dependent on, for example, dose, criterion level, sample timing, clinical factors such as hospitalization diet and age. These studies have been comprehensively reviewed (11, 32, 33). This study used 1 mg of dexamethasone at 2200 for the DST. The choice of dose and the time of blood sampling were based on our clinical experience from our previous studies with psychiatric patients and from the literature. As criterion for non-suppression of cortisol, three cut-off points were used. The choice of cut-off point influences the sensitivity and specificity of the test. Thus, results from one study showed that going from a criterion of cortisol > 82 nmol/l to > 165 nmol/l decreased the sensitivity from 48% to 37% but increased the specificity from 81% to 90% (35). Most investigators have used 139 nmol/l (5 µg/dl) or 166 nmol/l (6 µg/dl). Our previous studies used 200 nmol/l, a limit that was based on our experiences from patients with hypothalamic-pituitary disorders.

CRH was isolated and characterized from sheep hypothalami in 1981 (34) and became available for clinical studies one year later. During recent years, rat CRH, identical to human CRH, has become available for clinical practice. However, ovine CRH is still used because of its longer half-life and duration of action. This study used human instead of ovine CRH to achieve more physiological conditions. Most investigators during recent years have performed the CRH test with the administration of either 100 µg or 1 µg per kilogram body weight of synthetic human or ovine CRH by intravenous injection. This study used a somewhat smaller dose of CRH to increase the possibility of separating patients having a possible hypersecretion. The dose chosen induces significant effects on ACTH in healthy subjects (35). The CRH injection was given at 1630, a time when the HPA axis is less active than in the morning. In most studies, including our previous studies about HPA axis function, the laboratory results from patients with major depressive disorder were compared with those from normal controls. However, this may mask differences because about half of the patients have apparently normal function of the HPA axis. This study therefore chose only patients with major depressive disorders and chose to compare the ACTH and cortisol response to CRH administration between the suppressors and the nonsuppressors.

The role of CRH in depressive illness has been studied by many investigators during recent years. Their studies have recently been comprehensively reviewed (37, 38). The initial finding from the CRH studies showed a blunted ACTH response to ovine CRH (16) and human CRH (39) in depressed patients compared with healthy controls. Reduced ACTH response to CRH administration has also been shown by others (40, 41). The patients in these studies were compared with healthy controls, but the outcome of the DST was not reported. The ACTH release after ovine CRH administration was investigated in 8 patients in depression and after recovery. All patients had nonsuppressed cortisol values (> 50 ng/ml) after an oral dose of 1 mg dexamethasone during depression and suppressed adequately (cortisol < 50 ng/ml) after clinical remission, following antidepressant treatment. The mean ACTH was indiscriminate at both test sessions (42).

Hypercortisolemia is one of the most consistent neuroendocrine disturbances in patients with depression and nonsuppression after dexamethasone administration. This increase in cortisol may result, at least in part, from adrenocortical hyperplasia and hyperresponsiveness to ACTH (13–15, 40). This study found no differences between the suppressors and nonsuppressors in cortisol levels just prior to the CRH administration or 120 min after the injection. The separation between cortisol levels and ACTH release after CRH has been observed by others and the results have been discussed and reviewed (37, 43). Chronically increased CRH stimulation resulted in a hyperfunction of the adrenal cortex by an activation of the pituitary. The pituitary will thus receive an increased stimulation from the hypothalamus and a negative feedback from the adrenal cortex, which in turn, would result in normal to low levels of ACTH, but ACTH high enough to perpetuate hypercortisolism. Our finding of a significant higher basal level of ACTH among nonsuppressors at the low cut-off point indicates a more complex

relationship than can be explained by negative feedback. The separation may involve both an altered glucocorticoid receptor and CRH receptor sensitivity and function at the pituitary level plus increased CRH secretion in depression.

The pathophysiological mechanism(s) behind the disturbances in the HPA axis in the nonsuppressors is not known. The disturbances may involve the limbic-hypothalamus system, the pituitary, and/or the adrenal cortex. Several hypotheses have been presented, discussed, and reviewed (11, 32, 36, 44, 45). The hypotheses have involved neurotransmitter systems as acetylcholine, serotonin, and noradrenalin (46, 47). That depression is a state of opiodergic deficiency was also suggested (48). The involvement of other ACTH stimulatory agents as vasopressin, angiotensin 11, vasoactive intestinal polypeptide (VIP), prostaglandins and β-endorphin have also been suggested (49, 50).

In conclusion, it now seems to be well established that about half of the patients with major affective disorders have signs of disturbances in the HPA axis. The disturbances involve hypercortisolemia, an adrenal hyperresponsiveness to ACTH, probably an increased CRH stimulation of the pituitary, and a receptor change at the pituitary level. The mechanism behind the increased CRH stimulation may involve alterations in the classical neurotransmitter systems acetylcholine, serotonin and noradrenalin plus impaired opioid inhibition and/or other ACTH stimulatory agents.

We recommend that the patients with major depression not only be compared with healthy controls but also subdivided by their response to the DST, because about half of the patients have an apparently normal function of the HPA axis. Important differences may be masked if they are not subdivided.

Acknowledgements

This work was supported by the Karolinska Institute, the Gadelius Foundation, the Swedish Medical Association and the Swedish Medical Research Council (Grant 3371). We thank Nurse Mariann Zettergren and the staff at ward 5 of the Department of Psychiatry for excellent help and technical assistance.

References

1. Reus VI, Joseph MS, Dallman MF. ACTH levels after the dexamethasone suppression test in depression. N Engl J Med 1982: 306 (4): 238–239.
2. Nasr SJ, Rogers C, Pandrey G, Altman EG, Gaviria FM, Davis JM. ACTH and dexamethasone suppression test in depression. Biol Psychiatry 1983: 18: 1069–1073.
3. Linkowski P, Mendlewicz J, Leclercq R et al. The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. J Clin Endocrinol Metab 1985: 61: 429–437.
4. Roy A, Gold P, Pickar D, Wolkowitz OM, Chrousos G, Paul SM. Pre- and post-dexamethasone plasma ACTH levels in depressed patients and normal controls. J Affective Disord 1986: 10: 95–99.
5. Sachar EJ, Hellman L, Fukushima DK, Gallagher TF. Cortisol production in depressive illness. Arch Gen Psychiatry 1970: 23: 289–298.
6. Winokur A, Amsterdam J, Caroff S, Snyder PJ, Brunswick D. Variability of hormonal responses to a series of neuroendocrine challenges in depressed patients. Am J Psychiatry 1982: 139: 39–44.
7. Halbreich U, Asnis GM, Shindledecker R, Zumoff B, Nathan S. Cortisol secretion in endogenous depression. I. Basal plasma levels. Arch Gen Psychiatry 1985: 42: 904–908.
8. Pfohl B, Sherman B, Schlechte J, Stone R. Pituitary adrenal axis rhythm disturbances in psychiatric depression. Arch Gen Psychiatry 1985: 42: 897–903.
9. Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression. I. Limbic system-adrenocorticol dysfunction. Arch Gen Psychiatry 1976 a: 33: 1039–1044.
10. Stokes PE, Stoll PM, Koslow SH et al. Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. Arch Gen Psychiatry 1984: 41: 257–267.
11. Arana GW, Mossman G. The dexamethasone suppression test and depression. Endocrinol Metab Clin North Am 1988: 17: 2: 21–39.
12. Carroll BJ, Curtis GC, Mendels J. Cerebrospinal fluid and plasma-free cortisol concentrations in depression. Psychol Med 1976: 6: 235–244.
13. Amsterdam JD, Winokur A, Abelman E, Lucki J, Rickels K. Cosyntropin (ACTH 1–24) stimulation test in depressed patients and healthy subjects. Am J Psychiatry 1983: 140: 907–909.
14. Amsterdam JD, Marinelli DL, Ager P, Winokur A. Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers. Psychiatry Res 1987: 21: 189–197.
15. Jaeckle RS, Kathol RG, Lopez J, Meller WH, Krummel SJ. Enhanced adrenal sensitivity to exogenous cosyntropin (ACTH a 1–24) stimulation in major depression. Arch Gen Psychiatry 1987: 44: 233–240.
16. Gold PW, Chrousos G, Kellner C et al. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. Am J Psychiatry 1984: 141: 619–627.
17. Holsboer F, Gerken A, von Bardeleben U et al. Human corticotropin-releasing hormone in depression – correlation with thyrotropin secretion following thyrotropin-releasing hormone. Biol Psychiatry 1986: 21: 601–611.
18. Lopez JF, Kathol RG, Jaeckle RS, Meller W. The HPA axis response to insulin hypoglycemia in depression. Biol Psychiatry 1987: 22: 153–166.
19. Nemeroff CB, Widerlöv E, Bissette G et al. Elevated concentration of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 1984: 222: 1342–1344.
20. 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: 873–877.
21. Roy A, Pickar D, Paul S, Doran A, Chrousos GP, Gold PW. CSF corticotropin-releasing hormone in depressed patients and normal control subjects. Am J Psychiatry 1987: 144: 641–645.
22. France RD, Urban B, Krishnan KRR et al. CSF corticotropin-releasing factor-like immunoreactivity in chronic pain patients with and without major depression. Biol Psychiatry 1988: 23: 86–88.
23. Arato M, Banki CM, Bisette G, Nemeroff CB. Ele-

vated CSF CRF in suicide victims. Biol Psychiatry 1989: 25: 355–359.
24. Nemeroff CB, Owens MJ, Bisette G, Andorn AC, Stanley M. Reduced corticotropin-releasing factor binding sites in the frontal cortex of suicide victims. Arch Gen Psychiatry 1988: 45: 577–579.
25. Beck-Friis J, Ljunggren JG, Thorén M, von Rosen D, Kjellman BF, Wetterberg L. Melatonin, cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. Psychoneuroendocrinology 1985: 10: 173–186.
26. Beck-Friis J, Kjellman BF, Aperia B et al. Serum melatonin in relation to clinical variables on patients with major depressive disorder and a hypothesis of a low-melatonin syndrome. Acta Psychiatry Scand 1985: 71: 319–330.
27. Kjellman BF, Ljunggren JG, Beck-Friis J, Wetterberg L. The effect of TRH on TSH and prolactin levels in affective disorders. Psychiatry Res 1985: 14: 353–363.
28. Undén F, Ljunggren JG, Beck-Friis J, Kjellman BF, Wetterberg L. Hypothalamic-pituitary-gonadal axis in major depressive disorders. Acta Psychiatr Scand 1988: 78: 138–146.
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd edn., revised. Washington, DC: APA, 1987.
30. Hamilton M. Development of a rating scale for primary depressive illness. Br J Clin Psychol 1967: 6: 278–296.
31. Asberg M, Perris C, Schalling D, Sedvall G. The CPRS-development and applications of a psychiatric rating scale. Acta Psychiatr Scand 1978 (suppl): 271: 5–27.
32. American Psychiatric Association. The dexamethasone suppression test: an overview of its current status in psychiatry. Am J Psychiatry 1987: 144: 1253–1262.
33. Extein I, Pottash ALC, Gold MS. Number of cortisol time points and dexamethasone suppression test sensitivity for major depression. Psychoneuroendocrinology 1985: 10: 281–288.
34. Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981: 213: 1394–1397.
35. Schüermeyer TH, Averginos PC, Gold PW et al. Human corticotropin-releasing factor in man: pharmacokinetic properties and dose response of plasma adrenocorticotropin and cortisol secretion. J Clin Endocrin Metab 1984: 59: 1103–1108.
36. Braddock L. The dexamethasone suppression test – fact and artifact. Br J Psychiatry 1986: 148: 363–374.
37. Holsboer F. Psychiatric implications of altered limbic-hypothalamic-pituitary-adrenocortical activity. Eur Arch Psychiatry Neurol Sci 1989: 238: 302–322.
38. Licinio J, Gold PW. Role of corticotropin-releasing hormone in depressive illness. In: Grossman A, ed. Bailliere's clinical endocrinology and metabolism. 1991: 5: 51–58.
39. Holsboer F, von Bardeleben U, Gerken A, Stalla GK, Müller OA. Blunted corticotropin and normal cortisol responses to human corticotropin-releasing factor in depression. N Engl J Med 1984: 11: 1127–1132.
40. Gold PW, Loriaux DL, Roy A et al. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnosis implications. N Engl J Med 1986: 314: 1329–1335.
41. Holsboer F, Gerken A, Stalla GK, Müller OA. Blunted aldosterone and ACTH release after human CRH administration in depressed patients. Am J Psychiatry 1987: 144: 229–231.
42. Holsboer F, Gerken A, Stalla GK, Müller OA. ACTH, cortisol and corticosterone output after ovine corticotropin-releasing factor challenge during depression and after recovery. Biol Psychiatry 1985: 20: 276–286.
43. Stokes PE, Sikes CR. The hypothalamic-pituitary-adrenocortical axis in major depression. Endocrinol Metab Clin North Am 1988: 17: 1–19.
44. Delbende C, Delaure H, Lefebvre D. Glucocortoids, transmitters and stress. Br J Psychiatry 1992: 160 (suppl): 24–34.
45. Nemeroff CB. New vistas in neuropeptide research in neuropsychiatry: focus on corticotropin-releasing factor. Neuropsychopharmacology 1992: 6: 69–75.
46. Carroll BJ, Greden JF, Haskett RF et al. Neurotransmitter studies of neuroendocrine pathology in depression. Acta Psychiatr Scand 280 (suppl) 1980: 183–199.
47. Sachar EJ. Endocrine abnormalities in depression. In: Paykel ES, ed. Handbook of affective disorders. New York: Churchill Livingstone, 1982: 191–201.
48. Zis AP, Garland JE. Opioid peptides and depression: the neuroendocrine approach. In: Grossman A, ed., Bailliere's clinical endocrinology and metabolism. 1991: 5: 97–117.
49. Akner G, Ljunggren JG, Kjellman BF, Undén F, Wetterberg L. Adrenocorticotropin and cortisol response to lysine vasopression in relation to the outcome of the dexamethasone suppression test in major depressive disorder. Acta Psychiatr Scand 1988: 77: 404–410.
50. Maclean DB, Jackson IMD. Molecular biology and regulation of the hypothalamic hormones. In: Sheppard MC, ed. Baillière's clinical endocrinology and metabolism. 1988: 2: 835–868.