Glucocorticoids decrease thyrotropin-releasing hormone messenger ribonucleic acid expression in the paraventricular nucleus of the human hypothalamus

Alkemade, A.; Ummehopa, U.A.; Wiersinga, W.M.; Swaab, D.F.; Fliers, E.

Link to publication

Glucocorticoids Decrease Thyrotropin-Releasing Hormone Messenger Ribonucleic Acid Expression in the Paraventricular Nucleus of the Human Hypothalamus

A. Alkemade, U. A. Unmehopa, W. M. Wiersinga, D. F. Swaab, and E. Fliers

Netherlands Institute for Brain Research (A.A., U.A.U., D.F.S., E.F.), 1105 AZ Amsterdam, The Netherlands; and Department of Endocrinology and Metabolism (A.A., W.M.W., E.F.), Academic Medical Center, University of Amsterdam, 1100 DE Amsterdam, The Netherlands

The way glucocorticoids affect TRH mRNA expression in the paraventricular nucleus of the hypothalamus is still unclear. In view of its relevance for Cushing's syndrome and depression, we measured TRH mRNA expression in human hypothalami obtained at autopsy by means of quantitative TRH mRNA *in situ* hybridization. In corticosteroid-treated subjects (n = 10), TRH mRNA hybridization signal was decreased as compared with matched control subjects (n = 10) (Mann-Whitney *U* test, *P* = 0.02). By inference, hypercortisolism as present in patients with Cushing's syndrome or major depression may contribute to lower serum TSH or symptoms of depression by lowering hypothalamic TRH expression. (*J Clin Endocrinol Metab* 90: 323–327, 2005)

I N CLINICAL CONDITIONS such as Cushing's syndrome, nonthyroidal illness (NTI), and major depression, an endogenous hypercortisolism is often present. In these conditions changes in the hypothalamus-pituitary-thyroid (HPT) axis also occur (1–3). A possible role for glucocorticoids as attenuating modulators of the HPT axis has been proposed for patients with Cushing's disease (4) and major depression (5). In these patients complex associations occur between TSH and ACTH responses to specific stimulation with TRH and CRH (5). TRH neurons in the paraventricular nucleus (PVN) are involved in the neuroendocrine regulation of the HPT axis (6), and a clear correlation with thyroid hormone serum levels indicated that TRH in the PVN can be considered a major determinant of thyroid hormone status in patients with NTI (7). The mechanism by which glucocorticoids influence TRH gene expression in the PVN is still unclear, although a glucocorticoid receptor has been identified in TRH neurons in the PVN, and a glucocorticoid response element is present on the TRH gene (8). *In vitro* experiments have shown that dexamethasone can either stimulate or inhibit TRH expression in cultured hypothalamic neurons, dependent on the dose in the medium (9, 10). Dexamethasone treatment decreases hypothalamic CRH mRNA and TRH mRNA in the rat PVN, whereas opposite effects are observed after adrenalectomy (11). In humans glucocorticoids decrease TSH secretion (12), whereas TSH is increased during metyrapone-induced hypocortisolemia (13). No data were, however, present on the effects of glucocorticoids on the HPT axis at the level of the hypothalamus in humans. In the

present study, we investigated, therefore, the effect of corticosteroids on TRH mRNA in the PVN of the human hypothalamus. TRH mRNA was measured in corticosteroid-treated patients by means of *in situ* hybridization in combination with quantification by computer-assisted image analysis. For a matched control group, we studied subjects without corticosteroid treatment and without a primary psychiatric or neurological disease.

Subjects and Methods

Subjects

We studied the hypothalamus of 10 subjects that were treated with corticosteroids until death and 10 matched controls. Doses of corticosteroids varied among patients but exceeded the normal daily production rate of 20 mg hydrocortisone in at least eight of 10 cases (14). Daily doses and cortisol equivalents are presented in Table 1 (15). Brain material was obtained from The Netherlands Brain Bank at The Netherlands Institute for Brain Research in accordance with the formal permission for a brain autopsy and the use of human brain material and clinical information for research purposes. All the brains were systematically investigated by a neuropathologist. Exclusion criteria for corticosteroid-treated patients were: 1) use of antiepileptics, dopamine, or opiates within 4 wk before death or use of amiodarone; 2) known thyroidal disease; 3) mechanical ventilation; and 4) psychiatric or neurodegenerative disease. Patients and control subjects were matched for sex and, as closely as possible, severity and duration of fatal illness in an attempt to match for possible interference by NTI (7, 16). Exclusion criteria for control subjects were identical with the addition of corticosteroid treatment within 4 wk before death. Clinicopathological data are presented in Table 1.

Histology

Hypothalami were fixed in 10% phosphate-buffered formalin at room temperature for 3–14 wk. Tissues were dehydrated in a graded ethanol series, cleared in xylene, and embedded in paraffin. Coronal serial sections (6 μm) were made from the level of the lamina terminalis to the mammillary bodies. Depending on availability, either the left or right hemihypothalamus was used. Every 100th section was collected on a chromealum gelatin-coated slide with 0.5% BSA (Sigma, Zwijndrecht, The Netherlands) in distilled water followed by Nissl staining (0.5%

TABLE 1. Clinicopathological data of the subjects

Subject no.	Sex	Age (yr)	PMD	Fix	Side	Corticosteroids; daily dose; cortisol equivalents, duration, and indication for treatment	Cause of death; clinical diagnoses; duration of fatal illness	TRH mRNA values (a.u.)
99125	F	40	10	98	L	Methylprednisolone; 1000 mg; 5000 mg, 3 d before death for exacerbation systemic lupus erythematosus, in addition to chronic prednisone	Multi-organ failure; renal insufficiency, systemic lupus erythematosus, sepsis, corticosteroid induced diabetes; 3 wk	11.63
97156	F	77	2	47	R	None	Septic shock, icterus; metastasized pancreas carcinoma, sepsis; 3 wk	10.66
99096	F	65	14	91	L	Dexamethasone; 12 mg; 320 mg, since 17 d before death for pancytopenia	Hypovolemic shock; pharynx carcinoma, upper intestinal tract bleeding, unsuccessful resuscitation; 2 d	8.01
98024	F	49	16	31	L	None	Shock; probably cardiac failure, myelodysplastic syndrome, acute myeloid leukemia, type II diabetes; 3 d	13.49
98095	F	75	nd	63	R	Prednisone; 40 mg; 160 mg, 1 d before death for exacerbation COPD, in addition to chronic prednisone	Respiratory insufficiency; mycosis fungoides, chronic obstructive pulmonary disease, atrial fibrillation, ischemic heart disease, pneumonia; 1 d	10.10
93139	F	78	6	32	R	None	Respiratory insufficiency; pneumonia, metastasized bronchus carcinoma, cachexia; 3 d	10.11
97162	M	38	11	37	L	Prednisone; 20 mg; 80 mg, chronic prednisone treatment for vasculitis in the framework of Wegener's granulomatosis	Sepsis; respiratory insufficiency, Wegener's granulomatosis, renal insufficiency, urothelium carcinoma, hyperparathyroidism; 1 wk	12.52
97066	M	55	4	27	R	None	Multi-organ failure; HIV, hepatosplenomegaly, Hodgkin lymphoma, cachexia; 1 wk	19.97
97075	M	33	18	32	L	Dexamethasone; 12 mg; 320 mg, 7 d before death for high intracranial pressure	Brain edema; multitrauma by traffic accident, subarachnoidal bleeding, subdural hematoma; 6 d	3.95
97082	M	36	29	42	R	None	Intracerebral hemorrhage; metastasized choriocarcinoma of the testis, coma and hemi-paresis, due to intracerebral hemorrhage; 6 d	9.85
93133	M	64	8	30	L	Prednisone; 80 mg; 320 mg, chronic prednisone as palliative pain therapy in preterminal phase	Subarachnoidal bleeding; chronic myeloid leukemia, thrombocytopenia, splenomegaly; 1 d	1.03
98072	M	79	17	31	L	None	Hemorrhage in the brain stem; generalized atherosclerosis, with moderate chronic renal failure, diverticulosis coli, hemorrhage in the brain stem; 1 d	10.32
93103	M	83	8	nd	L	Prednisolone; dose unknown; 11 d before death for exacerbation COPD	Respiratory insufficiency; unsuccessful resuscitation, chronic obstructive pulmonary disease, malignant tumor of the right lung; 1 d	2.42
94039	M	78	nd	88	L	None	Electromechanical dissociation during heart catheterization; ischemic heart disease, recent myocardial infarction; 2 d	5.89
90010	M	24	17	29	L	Corticosteroids; dose unknown; 13 d before death for pancytopenia	Pneumonia; AIDS, candidiasis, herpes, lymphoma, cytomegalovirus, acute renal insufficiency; 1 month	6.75
94109	M	82	5	32	L	None	Multi-organ failure; M. Kahler, metastasized prostate carcinoma, urosepsis, renal insufficiency; 6 wk	13.75
96419	M	29	7	nd	L	Prednisone; at least 10 mg; at least 40 mg, 6 d before death as immunosuppressive agent after kidney transplantation	Probable cardiac arrest; chronic renal insufficiency, kidney transplantation; 1 d	1.44
94076	M	78	8	24	L	None	Probable cardiac arrest; unsuccessful resuscitation, Bechterew's disease, atrial fibrillation, renal insufficiency; 1 d	5.30
94074	F	85	5	28	L	Prednisone; 20 mg; 80 mg, 1 wk for exacerbation COPD	Respiratory insufficiency; chronic obstructive pulmonary disease, pneumonia, left-sided pneumothorax; 2 wk	5.67
99046	F	89	5	36	L	None	Probable acute myocardial infarction; decompensatio cordis, severe left-sided cardiac failure based on mitral valve insufficiency and coronary sclerosis; 4 wk	13.13

F, Female; m, male; Fix, fixation period in days; L, left; R, right; nd, not determined; PMD, postmortem delay before fixation in hours; Side, side of the hypothalamus that was studied; COPD, chronic obstructive pulmonary disease.

thionine in distilled water) for the establishment of the anatomical boundaries of the PVN. Additional immunocytochemical staining for vasopressin was performed for more precise delineation of the rostral and caudal border of the PVN as described previously (17, 18).

In situ hybridization for TRH mRNA

In situ hybridization was performed through the entire PVN using a systematic random sampling procedure. Every 100th section of the area in which the PVN was located was mounted on RNase-free 2% amino-alkyl-silane-coated slides. The hybridization procedure has been described previously (19).

In short, sections were dried in a stove set at 37 C for at least 2 d. Sections were deparaffinized in xylene, brought through graded ethanols, treated with 0.2 M HCl, and washed in PBS. Subsequently sections were deproteinated with proteinase K (10 μg/ml, 37 C, 30 min). The protease treatment was stopped in glycine buffer and slides were washed in PBS. Probes were diluted in hybridization buffer. Seventy microliters of hybridization buffer containing 8×10^5 dpm of ^{35}S-labeled TRH probe complementary to bp 330–549 of the human prepro-TRH cDNA (10) was applied to each section. Sections were coverslipped and hybridized overnight at 66 C. Coverslips were removed in $2 \times$ standard saline citrate (SSC) at 37 C, and sections were washed sequentially for 45 min at 60 C in $1\times$ SSC, $0.1\times$ SSC, $0.01\times$ SSC, and finally three times for 1 h in $0.001\times$ SSC. Sections were dehydrated in 300 mM ammonium acetate (pH 5.5)/ethanol 100% at volume ratios of 1:1, 3:7, 1:9, and 0:1, respectively and dried in a stream of cool air for 5 min. Sections were aposed directly to autoradiography film (Amersham, Buckinghamshire, UK) and exposed for 2 d. The time of exposure was determined experimentally. Films were developed for 2.5 min in D-19 developer (Kodak) and fixed in Maxfix (Kodak) for 10 min. After rinsing in running tap water, the films were dried.

Sections were hybridized in two sessions within 1 wk using one batch of labeled probe. Matched couples of control subjects and subjects treated with corticosteroids were hybridized in the same session. We used RNase-treated sections (0.2 mg/ml RNase in PBS for 1 h at 37 C before protease treatment) as a negative control in both sessions.

Quantitative analysis of TRH mRNA in situ hybridization

For quantification of the TRH mRNA *in situ* hybridization signal, we used radioactive standards. The methods of densitometry and quantification have been published elsewhere (14). In short, gray values of the film autoradiograms were analyzed by computer-assisted densitometry using an Interaktives Bild-Analysen system image analysis system (Kontron Elektronik, Munich, Germany) and software developed at our institute. The relationship between the gray values and the amount of radioactivity was assessed with radioactive standards. The labeled area of the PVN and the structure-weighted, background-corrected mean density of each section were determined and used to estimate the total amount of radioactive label present in the PVN. This was used as a relative measure for the amount of TRH mRNA in the PVN and expressed in arbitrary units (a.u.).

Statistical analysis

Differences between groups (corticosteroid treated *vs.* control) were tested with a Mann-Whitney *U* test (0.05 level of significance). A multivariate regression analysis (stepwise, dependent variable total TRH mRNA hybridization signal; 0.05 level of significance) of the factors postmortem delay, fixation duration, side of the hypothalamus, and age was performed.

Results

All subjects showed a clear hybridization signal in the region of the PVN using the TRH mRNA antisense probe. The RNase-treated sections yielded a completely negative hybridization signal on the film autoradiograms, supporting specificity of the procedure. The intensity of the signal showed a strong interindividual variation (Fig. 1). The TRH mRNA hybridization signal was significantly decreased in
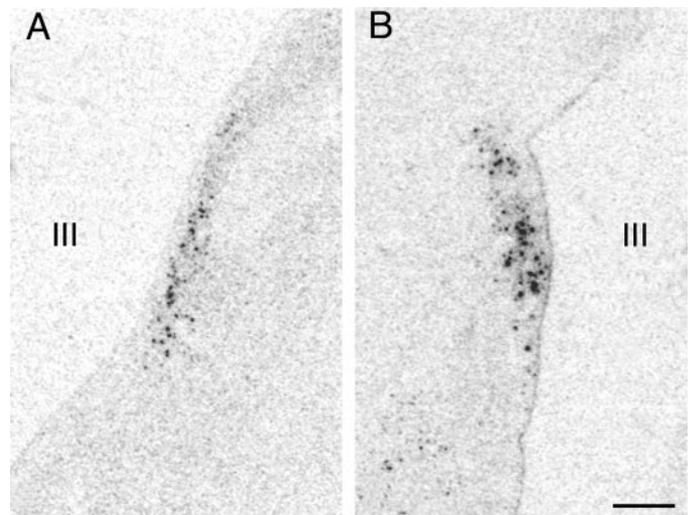

FIG. 1. Film autoradiograms of representative sections of a corticosteroid-treated subject, no. 96419 (A), showing weaker TRH mRNA hybridization signal than a control subject, no. 94076 (B). *Bar*, 1 mm.

subjects who were treated with corticosteroids (median 6.21 a.u.), compared with control subjects (median 10.49 a.u., $P = 0.02$) (Fig. 2).

A multivariate regression analysis of the factors postmortem delay, fixation duration, side of the hypothalamus, and age showed no influence of these factors on TRH mRNA hybridization signal.

Discussion

The specificity of the TRH cRNA probe was supported in an earlier study by displacement studies with unlabeled probe, by the absence of hybridization signal using a labeled sense probe and the absence of interfering homologies (19). In agreement with earlier studies (7), we observed a strong interindividual variation, which can be explained in part by NTI.

Borson-Chazot *et al.* (20) reported lateralization of TRH concentrations in the human hypothalamus, with a left prominence for TRH. However, lateralization was not observed by a later study in suicide victims (21). We studied
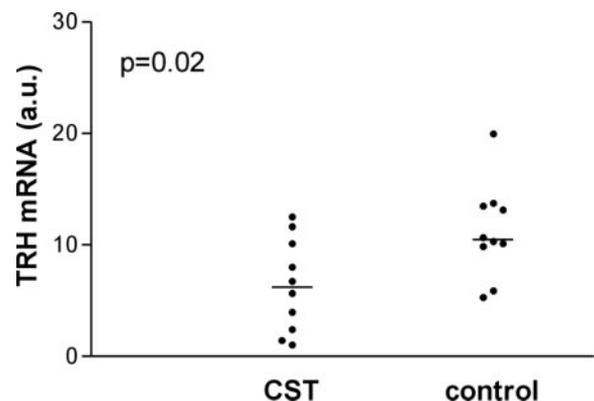

FIG. 2. TRH mRNA hybridization signals and medians in corticosteroid-treated subjects (CST) and controls. Each *dot* represents one subject. Statistical analysis was performed using a Mann-Whitney *U* test.

mostly the left side of the hypothalamus (n = 15) but also the right side (n = 5) when the left side of the PVN was not available for our research. A possible interference of lateralization was tested with a linear regression analysis but showed no effect.

TRH mRNA expression is influenced by nutritional status. In rats a decrease in TRH mRNA is observed during starvation (22). In the present study, two cachectic patients were included. Because these two patients were in the control group, the decrease in TRH mRNA expression in the corticosteroid-treated group may in fact have been underestimated in the present study.

Because discrete changes in thyroid hormone levels, including slightly lower serum free T_3, have been described in healthy elderly people, age can be considered a possible confounder for TRH mRNA in the hypothalamus (23). However, no effect of age has been observed in our previous studies on TRH expression in the human PVN (7, 19, 24), whereas NTI can be considered a major determinant of TRH expression. We therefore matched subjects in the present study for severity and duration of illness in an attempt to match for NTI rather than age. We did analyze a possible effect of age using a multivariate regression analysis but again found no effect on TRH mRNA in this study.

Cortisol equivalents in this study were based on peripheral action of glucocorticoids (15), whereas it is unknown what concentrations are reached in the brain. Rat studies have indicated that brain uptake of exogenous corticosteroids is very low (25), but postmortem studies in humans treated with corticosteroids have shown that pharmacological doses similar to the ones the patients in the present study received are able to diminish expression of CRH in PVN neurons (26).

The effect of glucocorticoids that we observed in the present study is in agreement with rat studies showing decreased TRH mRNA in the PVN after dexamethasone treatment (11). *In vitro*, however, variable effects have been described. Both stimulation and inhibition of TRH mRNA in hypothalamic cells cultures were observed, dependent on the concentration of dexamethasone in the medium (9, 10). The discrepancy between inhibitory effects *in vivo* and stimulatory effects *in vitro* of corticosteroids on TRH mRNA may be partly explained by an indirect effect of glucocorticoids. The absence of afferent input to cultured neurons indicates that glucocorticoids may affect the PVN *in vivo* directly as well as indirectly, *e.g.* via the hippocampus (27).

In the present study, we found a decrease in TRH mRNA expression in the PVN of corticosteroid-treated patients. This may explain somewhat lower serum TSH in patients treated with pharmacological doses of corticosteroids. By inference, endogenous hypercortisolism as may be present in patients with Cushing's syndrome, critical illness, and major depression (1–3) may also decrease TRH mRNA expression in the PVN. Indeed, decreased TRH mRNA has been reported by our group in the PVN of patients with nonthyroidal illness and in patients with major depression (7, 16). This decrease in TRH mRNA may be of importance in the pathogenesis of depression, which is often seen in patients treated with corticosteroids (28) and patients with Cushing's syndrome (29, 30). Because intrathecal administration of TRH in refractory depression has marked beneficial effects (31), a diminish-

ment of TRH may contribute to the signs and symptoms of depression.

References

1. **Rubello D, Sonino N, Casara D, Girelli ME, Busnardo B, Boscaro M** 1992 Acute and chronic effects of high glucocorticoid levels on hypothalamic-pituitary-thyroid axis in man. J Endocrinol Invest 15:437–441
2. **Dahl RE, Ryan ND, Puig-Antich J, Nguyen NA, al Shabbout M, Meyer VA, Perel J** 1991 24-Hour cortisol measures in adolescents with major depression: a controlled study. Biol Psychiatry 30:25–36
3. **Van den Berghe G, de Zegher F, Bouillon R** 1998 Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 83:1827–1834
4. **Bartalena L, Martino E, Petrini L, Velluzzi F, Loviselli A, Grasso L, Mammoli C, Pinchera A** 1991 The nocturnal serum thyrotropin surge is abolished in patients with adrenocorticotropin (ACTH)-dependent or ACTH-independent Cushing's syndrome. J Clin Endocrinol Metab 72:1195–1199
5. **Holsboer F, Gerken A, von Bardeleben U, Grimm W, Beyer H, Muller OA, Stalla GK** 1986 Human corticotropin-releasing hormone in depression—correlation with thyrotropin secretion following thyrotropin-releasing hormone. Biol Psychiatry 21:601–611
6. **Segerson TP, Kauer J, Wolfe HC, Mobtaker H, Wu P, Jackson IM, Lechan RM** 1987 Thyroid hormone regulates TRH biosynthesis in the paraventricular nucleus of the rat hypothalamus. Science 238:78–80
7. **Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF** 1997 Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 82:4032–4036
8. **Cintra A, Fuxe K, Wikstrom AC, Visser T, Gustafsson JA** 1990 Evidence for thyrotropin-releasing hormone and glucocorticoid receptor-immunoreactive neurons in various preoptic and hypothalamic nuclei of the male rat. Brain Res 506:139–144
9. **Luo LG, Bruhn T, Jackson IM** 1995 Glucocorticoids stimulate thyrotropin-releasing hormone gene expression in cultured hypothalamic neurons. Endocrinology 136:4945–4950
10. **Perez-Martinez L, Carreon-Rodriguez A, Gonzalez-Alzati ME, Morales C, Charli JL, Joseph-Bravo P** 1998 Dexamethasone rapidly regulates TRH mRNA levels in hypothalamic cell cultures: interaction with the cAMP pathway. Neuroendocrinology 68:345–354
11. **Kakucska I, Qi Y, Lechan RM** 1995 Changes in adrenal status affect hypothalamic thyrotropin-releasing hormone gene expression in parallel with corticotropin-releasing hormone. Endocrinology 136:2795–2802
12. **Samuels MH, Luther M, Henry P, Ridgway EC** 1994 Effects of hydrocortisone on pulsatile pituitary glycoprotein secretion. J Clin Endocrinol Metab 78:211–215
13. **Samuels MH** 2000 Effects of metyrapone administration on thyrotropin secretion in healthy subjects—a clinical research center study. J Clin Endocrinol Metab 85:3049–3052
14. **Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL** 1991 Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 72:39–45
15. **Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG** 1995 In: Goodman, Gilman's the pharmacological basis of therapeutics. 9th ed. New York: McGraw Hill; 1459–1486
16. **Alkemade A, Unmehopa UA, Brouwer JP, Hoogendijk WJ, Wiersinga WM, Swaab DF, Fliers E** 2003 Decreased thyrotropin-releasing hormone gene expression in the hypothalamic paraventricular nucleus of patients with major depression. Mol Psychiatry 8:838–839
17. **Swaab DF** 2003 The human hypothalamus: basic and clinical aspects. Part 1: nuclei of the human hypothalamus In: Aminoff MJ, Boller F, Swaab DF, eds. Handbook of clinical neurology. Vol 79. Amsterdam: Elsevier; 249–261
18. **Fliers E, Swaab DF, Pool CW, Verwer RW** 1985 The vasopressin and oxytocin neurons in the human supraoptic and paraventricular nucleus: changes with aging and in senile dementia. Brain Res 342:45–53
19. **Guldenaar SE, Veldkamp B, Bakker O, Wiersinga WM, Swaab DF, Fliers E**

1996 Thyrotropin-releasing hormone gene expression in the human hypothalamus. Brain Res 743:93–101

20. **Borson-Chazot F, Jordan D, Fevre-Montange M, Kopp N, Tourniaire J, Rouzioux JM, Veisseire M, Mornex R** 1986 TRH and LH-RH distribution in discrete nuclei of the human hypothalamus: evidence for a left prominence of TRH. Brain Res 382:433–436

21. **Jordan D, Borson-Chazot F, Veisseire M, Deluermoz S, Malicier D, Dalery J, Kopp N** 1992 Disappearance of hypothalamic TRH asymmetry in suicide patients. J Neural Transm Gen Sect 89:103–110

22. **Legradi G, Emerson CH, Ahima RS, Flier JS, Lechan RM** 1997 Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. Endocrinology 138:2569–2576

23. **Mariotti S, Barbesino G, Caturegli P, Bartalena L, Sansoni P, Fagnoni F, Monti D, Fagiolo U, Franceschi C, Pinchera A** 1993 Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab 77:1130–1134

24. **Fliers E, Noppen NW, Wiersinga WM, Visser TJ, Swaab DF** 1994 Distribution of thyrotropin-releasing hormone (TRH)-containing cells and fibers in the human hypothalamus. J Comp Neurol 350:311–323

25. **de Kloet ER** 1997 Why dexamethasone poorly penetrates in brain. Stress 2:13–20

26. **Erkut ZA, Pool C, Swaab DF** 1998 Glucocorticoids suppress corticotropin-releasing hormone and vasopressin expression in human hypothalamic neurons. J Clin Endocrinol Metab 83:2066–2073

27. **Jackson IM** 1995 Thyrotropin-releasing hormone and corticotropin-releasing hormone—what's the message? Endocrinology 136:2793–2794

28. **Mitchell A, O'Keane V** 1998 Steroids and depression. BMJ 316:244–245

29. **Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW, Chrousos GP** 1997 The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. J Clin Endocrinol Metab 82:912–919

30. **Gold PW, Licinio J, Wong ML, Chrousos GP** 1995 Corticotropin releasing hormone in the pathophysiology of melancholic and atypical depression and in the mechanism of action of antidepressant drugs. Ann NY Acad Sci 771:716–729

31. **Marangell LB, George MS, Callahan AM, Ketter TA, Pazzaglia PJ, L'Herrou TA, Leverich GS, Post RM** 1997 Effects of intrathecal thyrotropin-releasing hormone (protirelin) in refractory depressed patients. Arch Gen Psychiatry 54:214–222

Erratum

In the article "Specificity and Regioselectivity of the Conjugation of Estradiol, Estrone, and Their Catecholestrogen and Methoxyestrogen Metabolites by Human Uridine Diphospho-glucuronosyltransferases Expressed in Endometrium" by Johanie Lépine, Olivier Bernard, Marie Plante, Bernard Têtu, Georges Pelletier, Fernand Labrie, Alain Bélanger, and Chantal Guillemette (*The Journal of Clinical Endocrinology & Metabolism* **89**:5222–5232, 2004), there are two errors in Table 3. The relative V_{max} for the formation of 4-OHE1-3G by UGT1A8 was reported as 1975 pmol/min/mg but should have been reported as 197.5 pmol/min/mg. Similarly, the catalytic efficiency (V_{max}/K_m) should be 1.07 μl/min/mg instead of 10.7 μl/min/mg. *The authors regret the errors.*

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.