COMMENTARY

New Insights into the Role of Cortisol and the Glucocorticoid Receptor in Severe Depression

Belanoff et al (2002) reported in this issue of *Biological Psychiatry* that the antiglucocorticoid mifepristone is effective in treating psychotic depression. If replicated in a placebo-controlled study, this finding will have important implications for the treatment of mood disorders for several reasons. It provides a possible new treatment for psychotic depression, the most difficult of the depressions to treat. The importance of this report is further enhanced by the observation that mifepristone produced clinically relevant responses in some patients in a few days rather than weeks. The clinical manifestations of the syndrome of psychotic depression and its amelioration after the short-term interruption by a glucorticoid receptor antagonist suggests that cortisol is intimately involved in the pathophysiology of severe forms of depression. In this commentary, we discuss the role of cortisol during the stress response and mechanisms by which cortisol can set into motion positive reverberatory feedback loops among brain regions regulating emotion and cognition relevant to mood disorders. We also briefly comment on the implications of hypercortisolism for long-term medical consequences of depressive illness.

It should be noted at the outset that most patients with major depression are not hypercortisolemic when studied cross-sectionally; however, this does not rule out clinically significant excessive exposure to glucocorticoids. In contrast to Cushing's disease, hypercortisolism does not occur every day in depressed patients. For example, we have observed that urinary free cortisol excretion may be elevated for 21 days out of the month of depressed patients compared with 4–5 days out of the month for control subjects (Gold et al, unpublished observations). Moreover, when plasma cortisol levels are elevated in depression, they are likely to be alternatively elevated and normal at different times of day. These episodic phenomena reflect, in part, the finding that patients with major depression, in contrast to patients with Cushing's disease, have normal glucocorticoid negative feedback at the pituitary rather than at the hypothalamus (Gold and Chrousos 2002; Holsboer 2000). As a consequence of intact negative feedback at the pituitary, as plasma cortisol rises, plasma corticotropin (ACTH) levels fall in response to glucocorticoid negative feedback, followed by a fall in plasma cortisol; as cortisol falls, there is less glucocorticoid negative feedback at the pituitary, and ACTH rises once again. This phenomenon could lead to an underestimation of the rate of hypercortisolism in depression. Finally, we now know that it is essential for cortisol levels to fall to very low levels at night for several hours, below a threshold for harmfulness. Serious illnesses such as osteoporosis and hyperparathyroidism have occurred in patients given quantitatively normal glucocorticoid replacement that did not provide for a sufficient cortisol fall at night. Stressed patients and patients with depression have a flattened circadian rhythm at night with significantly less variation in the levels of nocturnal cortisol.

How Might Cortisol Contribute to Severe Depression?

Cortisol has significant interactions with the neurotransmitters, neuropeptides, and brain circuits associated with depressive symptomology. There is evidence, for several brain regions, of multiple positive feedback loops that may override multiple homeostats working to maintain hypothalmic-pituitary-adrenal (HPA) axis and stress homeostasis more generally. These data provide a framework to consider the putative antidepressant mechanisms of action for mifepristone.

Prefrontal Cortex

Drevets and colleagues found that the volume and metabolic activity of the left subgenual medial prefrontal cortex (mPFC) is reduced in major depression (Drevets et al 1997). Histopathologic studies revealed reduced grey matter volume and reduced glial numbers, without equivalent loss of neurons. The PFC functions include calculation of the likelihood of reward or punishment during threatening situations, shifting affect adaptively based on internal and external cues and facilitation of complex cognitive operations. The PFC also mediates cortical restraint on the amygdala (Davidson 2002), the HPA axis (Diorio et al 1993), and brain-stem noradrenergic nuclei (Gray and Bingaman 1996).

Cortisol administration to human subjects alters processes associated with PFC functions such as inhibitory control, attention regulation, and planning (Lupien et al 1999; Young et al 1999). In the nonhuman primate, cortisol impairs mPFC-mediated behavioral inhibition (Lyons et al 2000) and in rats causes a significant reorganization of PFC dendritic fibers (Wellman 2001). Lesioning of the left infralimbic region in the rat (analogous to the PFC) produces a pronounced activation of the

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HPA axis and sympathetic nervous system, whereas lesioning of the right profoundly diminishes HPA axis and sympathetic nervous system activity (Sullivan and Gratton 1999). Notably, it was on the left where Drevets and colleagues found loss of volume and metabolic activity in subgenual mPFC of depressed patients. The fact that cortisol impairs PFC function, which in turn leads to disinhibition of the HPA axis, is an example of a positive feedback loop in which cortisol leads to an activation of further cortisol secretion. Mifepristone may antagonize the effects of excessive cortisol on PFC structure and function and interrupt a maladaptive feed forward mechanism in severely depressed patients.

Amygdala

The amygdala is, of course, critically involved in the regulation of emotional behavior, a function highly relevant to severe depression. Depressed patients have increased amygdala metabolism on the left that has been positively correlated with depression severity and plasma cortisol levels in both unipolar and bipolar patients (Drevets et al 2002). During antidepressant treatment, the mean amygdala metabolism may be reduced in treatment responders, and elevated amygdala metabolism during remission has been associated with a high risk for the development of depressive relapse (Drevets 2001). In addition to its emotion-related effects, the amygdala inhibits the PFC (Davidson 2002) and activates both the HPA axis (Prewitt and Herman 1994) and brain-stem noradrenergic nuclei, including the locus coeruleus (LC; Gray and Bingaman 1996). Amygdala-mediated activation of the LC-noradrenergic system further enhances cortisol secretion because norepinephrine (NE) is stimulatory to corticotropin releasing hormone (CRH).

Whereas the amygdala promotes hypercortisolism by these mechanisms, corticosteroids can enhance amygdala activity. Corticosterone administration to the rat increases the level of CRH mRNA in the central nucleus of the amygdala and the bed nucleus of the stria terminalis (Makino et al 1994, 1995; Shepard et al 2000). Cortisol also increases the effects of CRH on conditioned fear (Lee et al 1994) and, via stimulation of glucocorticoid (GR) receptors on the basolateral nucleus of the amygdala (BLA), facilitates the encoding of emotion-related memory (Roozendaal 2000). The BLA receives noradrenergic innervation from the nucleus tractus solitarius (NTS) and the LC (Fallon and Ciofi 1992). These cell bodies have very high densities of GRs in stressed animals (Morimoto et al 1996), indicative of the robust glucocorticoid–noradrenergic system functional interactions relevant to stress and depression.

Thus, the functional relationships, outlined here, between hypercortisolism and the amygdala may result in a self-perpetuating cycle in which amygdala hyperactivity enhances cortisol release, and, in turn, high levels of cortisol increase amygdala activity. Mifepristone may mitigate the adverse effects of amygdala activation in depression by blocking the actions of glucocorticoids on GR receptors in the amygdala. Consequently, this may reduce the deleterious clinical effects of amygdala hyperactivity on the PFC, hippocampus, and brain-stem sites.

Hippocampus

Several groups have found that the volume and the function of the hippocampus is reduced in patients with major depression (Bremner et al 2000; Sheline et al 1996). This reduction, which appears to be greatest in patients with the longest duration of illness (Sheline et al 1999) may be, in part, mediated by hypercortisolism. Patients with Cushing's disease exhibit significant loss of hippocampal volume and increased volume of the third ventricle, which are at least partially reversible after correction of the hypercortolism (Borduau et al 2002). Depressed affect, memory dysfunction, and insomnia are also characteristic of Cushing's syndrome and are correlated positively with plasma cortisol levels (Starkman et al 1981). In addition to its key role in memory function, the hippocampus also contributes to glucocorticoid-mediated negative feedback on the HPA axis through mineralocorticoid (MR) receptors that are high affinity and low capacity and respond to low basal cortisol levels and GR receptors that are low affinity and high capacity and respond to higher levels of cortisol during stress (Bradbury et al 1994; Kellendonk 2002). Glucocorticoid-mediated damage to the hippocampus activates an important reverberatory feedback loop in which excess cortisol secretion leads to a change that further promotes cortisol secretion. Short-term blockade of glucocorticoid receptors by mifepristone may help reset a putative dysfunctional glucocorticoid negative feedback site in depressed patients.

Hippocampal function is very much influenced by glucocorticoid concentration. Acutely, glucocorticoids regulate neuronal excitability and alter hippocampal-dependent behaviors, such as spatial memory. Chronically, glucocorticoids impair hippocampal morphology and lead to cognitive impairment. High levels of glucocorticoids activate both MR and GR receptors and inhibit neuronal excitability (Joels and deKloet 1992); GR activation favors long-term depression and suppresses long-term potentiation (Pavlides et al 1995, 1999). It is possible that mifepristone antagonizes these actions and, under conditions of high cortisol, can improve cognition. This hypothesis remains to be tested.

Hypothalamus

Radeshaar and colleagues found that in brains taken from patients with major depression who had committed suicide, there was a greater number of paraventricular neurons expressing CRH mRNA compared with control subjects. Moreover, this increase in CRH-containing neurons occurred predominantly in the separate subpopulation of CRH neurons that send descending projections to brain-stem noradrenergic nuclei (Raadsheer et al 1995). Notably, glucocorticoids increase rather than decrease mRNA levels in this separate descending hypothalamic CRH pathway (Swanson and Simmons 1989). By activating LC neurons, CRH increased noradrenergic activity at LC projection sites. Thus, cortisol, via CRH, activates NE secretion. There is also evidence that NE activates the HPA axis (Calogero et al 1988). Taken together, cortisol may drive a positive reverberatory feedback loop between hypothalamic CRH and brain-stem norepinephrine-containing neurons, thereby setting into motion NE-mediated activation of cortisol secretion.

Cortisol also exerts negative feedback effects on hypothalamic CRH neurons that send terminals to the median eminence for activation of the pituitary-adrenal axis. In depressed patients, the negative feedback loop fails to bring cortisol levels back to their homeostatic levels, either secondary to loss of glucocorticoid negative feedback or to an overriding stimulus to activation of the HPA axis such as CRH and NE. In severely depressed hospitalized patients, around-the-clock plasma cortisol and CSF NE levels are higher, even throughout the night (Wong et al 2000). The diurnal patterns of NE were virtually identical in both patients and control subjects, and a significant positive correlation was found between plasma cortisol and CSF NE that was as significant as that seen between plasma ACTH and plasma cortisol (Wong et al 2000). The persistence of this robust correlation may reflect, in part, an inhibited mPFC, an activated amygdala, an activated CRH hypothalamic pathway to the brain stem, and an activated LC. As noted, each pathway leads not only to the stimulation of cortisol, but also, in turn, is stimulated by cortisol.

Under some circumstances, glucocorticoids inhibit noradrenergic function and the sympathetic nervous system. For example, cortisol released during hypoglycemia in diabetic patients is thought to acutely restrain the sympathetic nervous system, thereby interfering with an important counterregulatory mechanism (McGregor et al 2002). Thus, it is possible that the positive relationships between CSF NE and plasma cortisol reflect an intense activation of the CRH and LC-NE systems that override glucocorticoid-mediated restraint of the norepinephrine release at the level of the hypothalamus.

The specific role of the GR in mediating the effect of cortisol on hypothalamic CRH concentrations remains to be established. In transgenic mice expressing antisense RNA against GR, resulting in reduced, but not absent, GR function, there was a reduction in CRH neurons in the paraventricular nucleus (PVN) of the hypothalamus with no effect on corticosterone levels (Dijkstra et al 1998). In contrast, complete inactivation of the GR gene in the central nervous system of mice produces an increase in CRH production in the PVN and in plasma corticosterone and no change in CRH levels in the central nucleus of the amygdala (Tronche et al 1999). It is noteworthy that both strains of mice exhibit a phenotype characterized by reduced anxiety, suggesting a role for the GR in the regulation of emotional behavior (Gass et al 2001). Determination of whether these observations are relevant to the clinical effects of mifepristone will require further study.

Medical Consequences of Hypercortisolemia Associated with Depression

Major depression is associated with an increase in mortality, independent of suicide, smoking, and other risk factors for poor health (Wulsin et al 1999). Furthermore, major depression appears to be an independent risk factor for the development of coronary heart disease and osteoporosis and alters the prognosis of these disorders as well as other medical disorders such as diabetes. Elevated cortisol may be a mediating factor in these relationships. Glucocorticoids exist at or near the center of a pathophysiologic circuit that leads to catabolism of bone and to changes in endocrine, metabolic, proinflammatory, and hemostatic mediators that enhance susceptibility to cardiovascular disease.

Cortisol exerts many effects that promote coronary artery disease. Cortisol inhibits the growth hormone (GH) and gonadal axes. GH deficiency, if established in major depression, is important because the relative risk for premature cardiovascular disease in adults with idiopathic GH deficiency is greater than twofold (Erfurth et al 1999; Hew et al 1998). Cortisol is a potent stimulus to visceral fat, a 2- to 3-kg, highly metabolically active organ, the hypertrophy of which has many adverse effects. Inhibition of the GH and gonadal axes exacerbates visceral fat accumulation. Excess visceral fat leads to dyslipidemia and, along with hypercortisolism, to insulin resistance, hyperinsulinism, and their sequellae (Gold and Chrousos 2002). Theoretically, increases in visceral fat may be cumulative over repeated depressive episodes and therefore have adverse metabolic effects even during apparent remissions. Although patients with major depression may be resistant to the effects of insulin in promoting glucose-transport, they are not usually resistant to any other insulin effects, including sympathetic nervous system (SNS) ac-

tivation, increased renal sodium retention, hypertrophy of vascular smooth muscle, release of potentially large quantities of proinflammatory cytokines from adipose tissue, activation of coagulation factors such a favor VIII, and inhibition of the most potent endogenous antifibrinolytic compound, plasminogen activator inhibitor factor-1 (API-1).

Patients with major depression have many risk factors for loss of bone density including HPA axis activation, suppression of the GH and reproductive axis, and NE-mediated activation of the release of proinflammatory cytokines. Michelson and colleagues reported that a subgroup of approximately 30% of premenopausal women with major depression showed preosteporotic (osteopenia) or osteoporotic changes in bone mineral density (Michelson et al 1996). Normally, progressive bone loss begins at the age of 28–30. This subgroup of subjects had already lost an average of 16% of bone below peak density at an average of 41. If bone density peaked at age 28, their rate of loss would be approximately 1.5% per year. This rate, if continued, would lead to severe osteoporosis at a relatively early age because bone, once lost, cannot be regained. Thus, bone loss in recurrent depression is cumulative. It should be noted that bone loss during glucocorticoid administration occurs relatively quickly and can be maximal after an interval as short as 3–4 months. Perhaps, specific antiglucorticoid therapies for depression may be particularly useful in reducing the medical consequences of depression associated with hypercortisolemia.

If confirmed, the therapeutic effects of mifepristone in psychotic depression will teach us a great deal about the roles of cortisol in the pathophysiology of not only psychotic depression but of depression more generally as well. As discussed, a general motif among mediators of the response to physical or emotional stress is amplification of the stress system response (especially that of the glucocorticoids) at multiple loci via the emergence of multiple positive feedback loops. Such amplifications are likely operative in some forms of severe depression and defeat multiple counterregulatory elements. The sustained activation of the HPA axis and a host of related mediators is a highly abnormal event. Our hope is that agents that influence specific components of glucocorticoid receptor interaction with other depression relevant neural and endocrine systems will refine the capacity to alter the pathologic effects of glucocorticoids in severe depression without adversely affecting most other HPA axis targets. The short-term amelioration of psychotic depression with mifepristone may represent a paradigm shift in the treatment of depression. The authors should be congratulated on a potentially extremely important contribution.

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References

Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu E-E, Schold C, Schatzberg AF (2002): An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry,* 386–392.

Borduau I, Bard C, Noel B, Leclerc I, Cordeau MP, Belair M, et al (2002): Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. *J Clin Endocrinol Metab* 87:1949–1954.

Bradbury MJ, Akana SF, Dallman MF (1994): Roles of type I and II corticosteroid receptors in regulation of basal activity in the hypothalamo-pituitary-adrenal axis during the diurnal trough and the peak: Evidence for a nonadditive effect of combined receptor occupation. *Endocrinology* 134:1286–1296.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HI, Charney DS (2000): Hippocampal volume reduction in major depression. *Am J Psychiatry* 157:115–118.

Calogero AE, Gallucci WT, Chrousos GP, Gold PW (1988): Catecholamine effects upon rat hypothalamic corticotropin-releasing hormone secretion in vitro. *J Clin Invest* 82:839–846.

Davidson RJ (2002): Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biol Psychiatry* 53:68–80.

Dijkstra I, Tilders FJ, Aguilera G, Kiss A, Rabadan-Diehl C, Barden N, et al (1998): Reduced activity of hypothalamic corticotropin-releasing hormone neurons in transgenic mice with impaired glucocorticoid receptor function. *J Neurosci* 18:3909–3918.

Diorio D, Viau V, Meaney MJ (1993): The role of the medial prefrontal cortex (cingulated gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J Neurosci* 13:3839–3847.

Drevets WC (2001): Neuroimaging and neuropathological studies of depression: Implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol* 11:240–249.

Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2002): Glucose metabolism in the amygdala in depression: Relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav* 71:431–447.

Drevets WC, Price JL, Simpson JJ, Todd RD, Reich T, Vannier M, Raichle ME (1997): Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–827.

Erfurth EM, Bulow B, Eskilsson J, Hagmar L (1999): High incidence of cardiovascular disease and increased prevalence of cardiovascular risk factors in women with hypopituitarism not receiving growth hormone treatment: Preliminary results. *Growth Horm IGF Res* 9(suppl A):21–24.

Fallon JL, Ciofi P (1992): Distribution of monoamines within the amygdala. In: Aggleton J, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss, pp 94–114.

Gass P, Reichardt HM, Strekalova T, Henn F, Tronche F (2001): Mice with targeted mutations of glucocorticoid and mineralocorticoid receptors: Models for depression and anxiety? *Physiol Behav* 73:811–825.

Gold PW, Chrousos GP (2002): Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Mol Psychiatry* 7:254–275.

Gray T, Bingaman E (1996): The amygdala: corticotropin-releasing factor, steroids, and stress. *Crit Rev Neurobiol* 10:155–168.

Hew FL, O'Neal D, Kamarudin N, Alford FP, Best JD (1998): Growth hormone deficiency and cardiovascular risk. *Baillieres Clin Endocrinol Metab* 12:199–216.

Holsboer F (2000): The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23:477–501.

Joels M, deKloet ER (1992): Control of neuronal excitability by corticosteroid hormones. *Trends Neurosci* 15:25–30.

Kellendonk C, Gass P, Kretz O, Schutz G, Tronche F (2002): Corticosteroid receptors in the brain: Gene targeting studies. *Brain Res Bull* 51:73–83.

Lee Y, Schulkin J, Davis M (1994): Effect of corticosterone on the enhancement of the acoustic startle reflex by corticotropin releasing factor (CRF). *Brain Res* 666:93–98.

Lupien SJ, Gillin CJ, Hauger RL (1999): Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose-response study in humans. *Behav Neurosci* 113:420–430.

Lyons DM, Lopez JM, Yang C, Schatzberg AF (2000): Stress-level cortisol treatment impairs inhibitory control of behavior in monkeys. *J Neurosci* 20:7816–7821.

Makino S, Gold PW, Schulkin J (1994): Effects of corticosterone on CRH mRNA and content in the bed nucleus of the stria terminalis; comparison with the effects in the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. *Brain Res* 675:141–149.

Makino S, Gold PW, Schulkin J (1995): Corticosterone effects on corticotropin-releasing hormone mRNA in the central nucleus of the amygdala and the parvocellular region of the paraventricular nucleus of the hypothalamus. *Brain Res* 640:105–112.

Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrouso S, et al (1996): Bone mineral density in women with depression. *N Engl J Med* 16:1176–1181.

McGregor VP, Banarer S, Cryer PE (2002): Elevated endogenous cortisol reduces autonomic neuroendocrine and symptom responses to subsequent hypoglycemia. *Am J Physiol Endocrinol Metab* 282:E770–777.

Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M (1996): Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: An immunohistochemical and in situ hybridization study. *Neurosci Res* 26:235–269.

Pavlides C, Kimura A, Magarinos AM, McEwen BS (1995): Hippocampal homosynaptic long-term depression/depotentiation induced by adrenal steroids. *Neuroscience* 68:379–385.

Pavlides C, McEwen BS (1999): Effects of mineralocorticoid and glucocorticoid receptors on long-term potentiation in the CA3 hippocampal field. *Brain Res* 851:204–214.

Prewitt CM, Herman JP (1994): Lesion of the central nucleus of the amygdala decreases basal CRH mRNA expression and stress-induced ACTH release. *Ann NY Acad Sci* 746:438–440.

Raadsheer FC, van Heerikhuise JJ, Lucassen PJ, Hoogendijk WJ, Tilders FJ, Swaab DF (1995): Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am J Psychiatry* 152:1372–1376.

Roozendaal B (2000): Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology* 25:213–238.

Sheline YI, Sanghavi M, Mintun MA, Gado MH (1999): Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 19:5034–5043.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW (1996): Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 93:3908–3913.

Shepard JD, Barron KW, Myers DA (2000): Corticosterone delivery to the amygdala increases corticotropin-releasing factor mRNA in the central amygdaloid nucleus and anxiety-like behavior. *Brain Res* 861:288–295.

Starkman MN, Schteingart DE, Schork MA (1981): Depressed mood and other psychiatric manifestations of Cushing's syndrome: Relationship to hormone levels. *Psychosom Med* 43:3–18.

Sullivan RM, Gratton A (1999): Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. *J Neurosci* 19:2834–2840.

Swanson L, Simmons D (1989): Differential steroid hormone and neural influences on peptide mRNA levels in CRH cells of the paraventricular nucleus: A hybridization histochemical study in the rat. *J Comp Neurol* 285:413–435.

Tronche F, Kellendonk C, Kretz O, Gass P, Anlag K, Orban PC, et al (1999): Disruption of the glucocorticoid receptor gene in the nervous system results in reduced anxiety. *Nat Genet* 23:99–103.

Wellman CL (2001): Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J Neurobiol* 49:245–253.

Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, et al (2000): Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: Relation to hypercortisolism and corticotropin-releasing hormone. *Proc Natl Acad Sci USA* 97:325–330.

Wulsin LR, Vaillant GE, Wells VE (1999): A systematic review of the mortality of depression. *Psychosom Med* 61:6–17.

Young AH, Sahakian BJ, Robbins TW, Cowen PG (1999): The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Pharmacology* 145:260–266.