

## Future therapeutic targets in mood disorders: the glucocorticoid receptor

RICHARD McQUADE and ALLAN H. YOUNG

**Background** The hypercortisolaemia and dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis associated with mood disorders have been attributed to a breakdown in the glucocorticoid-receptor-mediated negative feedback mechanism regulating HPA activity. Reinstating normal feedback may be therapeutic in mood disorders.

**Aims** To review the evidence for the involvement of the glucocorticoid receptor in the pathogenesis and treatment of mood disorders.

**Method** Medline and hand searches were carried out, selecting literature relevant to psychiatrists and psychopharmacologists.

**Results** A dysfunction in glucocorticoid receptors is integral to the HPA abnormalities of mood disorders. Antidepressant and mood-stabilising drugs can up-regulate glucocorticoid receptors, restoring glucocorticoid function. Preliminary clinical studies targeting the glucocorticoid receptor are encouraging.

**Conclusions** Drugs designed specifically to up-regulate glucocorticoid receptors may be integral to future strategies in treating mood disorders.

**Declaration of interest** None.

Kraepelin (1896) and Freud (1905) both regarded endocrinology as potentially important in the causation and treatment of major psychiatric disorders. However, early attempts to understand the relationship between the endocrine systems and psychiatric disorders failed because of a lack of appropriate methodology and scant knowledge of the complexity of the neural systems involved. With the substantial developments in the field of neuroendocrinology, it has become clear that the endocrine systems are strongly implicated in the pathophysiology of psychiatric disorders. In this article we review the possible role for glucocorticoid receptors in the disturbance of the hypothalamic–pituitary–adrenal (HPA) axis observed in mood disorders, and the implications of this for future therapeutics.

### HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The HPA axis is a multifaceted regulatory system which integrates neuronal and endocrine function. It can be defined as comprising the tissues of the hypothalamus, pituitary and adrenal cortex, and the regulatory inputs, releasing factors and hormones therein (see Fig. 1). In brief, the neurosecretory cells of the paraventricular nucleus (PVN) of the hypothalamus secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the microportal circulatory system of the pituitary stalk. These secretagogues induce the release of adrenocorticotrophic hormone (ACTH) from the anterior lobe of the pituitary into the systemic circulation; ACTH in turn promotes the release of the glucocorticoid cortisol from the adrenal cortex. Cortisol, in some respects the final product of the HPA axis, has a panoply of both central and peripheral effects mediated via at least two specialised glucocorticoid receptor subtypes: the high-

affinity type I receptor (or MR) and the low-affinity type II receptor (or GR).

### HPA regulation

Cells in the PVN secrete CRH, which is the driving force of the HPA axis; AVP only weakly stimulates ACTH by itself, but markedly potentiates the effects of CRH. The secretory cells in the PVN receive neuronal inputs from many brain regions, including amygdala, hippocampus and nuclei of the midbrain. Excitatory and inhibitory afferents, including those containing 5-hydroxytryptamine (5-HT), noradrenaline, acetylcholine, and both excitatory and inhibitory amino acids, have been demonstrated (Jones *et al*, 1987). In addition to these extrinsic regulatory inputs to the HPA axis, a crucial intrinsic autoregulatory mechanism also exists. Thus, endogenous cortisol, by binding to glucocorticoid receptors in the HPA axis tissues and the hippocampus, acts as a potent negative regulator of HPA activity (Sapolsky *et al*, 1986). The relative contribution of the two glucocorticoid receptor subtypes (GR and MR) in the regulation of HPA activity is as yet unclear. However, the high-affinity MRs putatively control low, basal levels of circulating cortisol, while the lower-affinity GRs come into play during circadian and stress-related peaks in cortisol (Jacobson & Sapolsky, 1991). This autoregulatory role of endogenous cortisol is crucial to the maintenance of the intrinsic homeostasis of the HPA axis (Sapolsky *et al*, 1986; Jacobson & Sapolsky, 1991). Furthermore, it is possible that by subtle changes in glucocorticoid receptor number or function the homeostatic ‘setpoint’ can be shifted and can contribute to the characteristic diurnal rhythm in circulating cortisol levels in healthy individuals.

### HPA dysfunction and psychiatric disorders

In the late 1950s Board and colleagues made the seminal observation that basal plasma cortisol levels of patients with depression are higher than those of healthy control subjects (Michael & Gibbons, 1963). This finding was replicated by Gibbons (1964), who further reported that, in the majority of patients, cortisol concentrations are lower during remission than they are during an acute illness episode. These initial observations

prompted much further research which has confirmed that hyperactivity of the HPA axis is associated with mood disorders. This HPA hyperactivity is revealed by increased levels of cortisol in plasma, urine and cerebrospinal fluid, exaggerated cortisol responses to ACTH and enlarged pituitary and adrenal glands in individuals suffering from severe mood disorders (Owens & Nemeroff, 1993). Measurement of plasma cortisol over 24 hours reveals that, compared with controls, people with depression exhibit a loss in the characteristic temporal rhythms in circulating cortisol secretion and show elevated nadir and flattening of circadian rhythm (Deuschle *et al*, 1997). Evidence of increased concentrations of CRH in the cerebrospinal fluid in patients with depression indicates that the hypercortisolaemia seen in mood disorders can be linked to over-secretion of CRH (Nemeroff *et al*, 1984). This CRH hypersecretion in mood disorders is further suggested by the blunted ACTH responses to a CRH challenge in people with depression and down-regulation of CRH receptors in post-mortem frontal cortices of suicide victims (Owens & Nemeroff, 1993; Holsboer & Barden, 1996). The above evidence strongly indicates that the hypercortisolaemia associated with mood disorders is a result of CRH hypersecretion. Although AVP hypersecretion

has also been postulated, as yet there is little direct evidence to implicate AVP abnormalities in mood disorders.

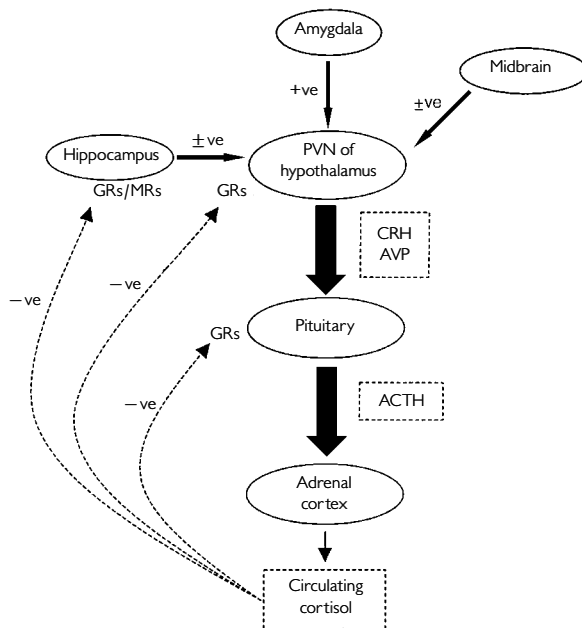
The hypersecretion of CRH and resultant hypercortisolaemia are thought to be a consequence of impaired feedback inhibition by endogenous corticosteroids (see Fig. 1). Since GRs in HPA axis tissues are integral to this feedback inhibition, this receptor is the prime suspect with respect to the genesis of HPA hyperactivity (Sapolsky *et al*, 1986). The dexamethasone suppression test (DST) is a measure of the functional integrity of the GR-mediated negative feedback mechanism. Here, the cortisol-suppressing activity of the synthetic glucocorticoid, dexamethasone, is an approximate indicator of GR status. Reports of cortisol non-suppression in response to dexamethasone in both unipolar and bipolar disorders do indeed suggest a primary GR abnormality in these disease states (Zhou *et al*, 1987; Swann *et al*, 1992). The methodology of the DST has been criticised, however, in that it fails to take into account the regulatory role of CRH, and subsequent modifications have resulted in the combined dexamethasone/CRH (dex/CRH) test (Heuser *et al*, 1994). The DST and the dex/CRH test consistently indicate dysfunction in HPA axis autoregulation in both unipolar and bipolar affective disorders. Furthermore, normalisation of responses in these tests on

remission of affective symptoms suggests that reinstating GR-mediated HPA autoregulation may be at least a correlate, if not the mechanism of action, of drugs used in the treatment of mood disorders (Zobel *et al*, 1999).

Although abnormalities downstream of the receptor could conceivably underlie the impaired GR function seen in mood disorders, evidence suggests that the dysfunction may simply be due to decreased receptor number. Thus, evidence of an abnormality of GRs in severe mood disorders has been directly shown by the recent post-mortem demonstration of reduced GR messenger RNA (mRNA) in the hippocampi of individuals suffering from unipolar and bipolar affective disorders (Webster *et al*, 1999). In addition, there is growing evidence that antidepressants and mood stabilisers stimulate GR mRNA expression in the brain, and in so doing, enhance the HPA autoregulation leading to lowered levels of CRH and cortisol.

### ANTIDEPRESSANTS, MOOD STABILISERS AND BRAIN GLUCOCORTICOID RECEPTORS

The modulation of GR number by treatments used in mood disorders was first shown by Pepin *et al* (1989), who reported that tricyclic antidepressants have the ability to increase GR mRNA in primary neuronal cultures. Subsequent *in vivo* studies have revealed that this increase in GR mRNA is in fact translated into an increase in receptor protein. Furthermore, this effect occurs not only with the tricyclic antidepressants desipramine, imipramine and amitriptyline but also with the mood stabiliser lithium and with electroconvulsive shock (Peiffer *et al*, 1991; Seckl & Fink, 1992; Reul *et al*, 1993; Przegalinski *et al*, 1993a,b) (see Table 1). The mechanism by which the antidepressants increase glucocorticoid receptors is as yet unclear and it is interesting that neither citalopram nor fluoxetine alters GR mRNA or binding capacity (Seckl & Fink, 1992; Rossby *et al*, 1995). This suggests that the selective serotonin reuptake inhibitor (SSRI) class of antidepressant may lack the ability to modulate GRs. The above evidence, together with the different clinical profiles of the drugs used to treat mood disorders,



**Fig. 1** Simplified schematic diagram of the hypothalamic–pituitary–adrenal (HPA) axis, describing regulation and negative feedback of cortisol via glucocorticoid receptors.

**Table 1** Effect of antidepressant treatments on type II glucocorticoid receptors (GRs) in various experimental systems

Treatment	System	Receptor mRNA	Receptor binding	Receptor activity	Reference
Desipramine	Neuronal culture	↑			Pepin <i>et al</i> , 1989
	Male rats	↑			Peiffer <i>et al</i> , 1991; Seckl & Fink, 1992
	GR-impaired transgenic mice	↑	↑		Pepin <i>et al</i> , 1992b
	Fibroblasts		↑	↑	Pepin <i>et al</i> , 1992a; Pariante <i>et al</i> , 1997
Amitriptyline	Neuronal culture	↑			Pepin <i>et al</i> , 1989
	Male rats	↑	↓ ↓		Seckl & Fink, 1992; Przegalinski <i>et al</i> , 1993a,b; Reul <i>et al</i> , 1993
Imipramine	Neuronal culture	No change			Pepin <i>et al</i> , 1989
	Male rats	↑	↑		Peiffer <i>et al</i> , 1991; Przegalinski <i>et al</i> , 1993a,b
Maprotiline	Neuronal culture	↑			Pepin <i>et al</i> , 1989
Fluoxetine	Male rats	No change			Rossby <i>et al</i> , 1995
Citalopram	Male rats	No change			Seckl & Fink, 1992
Lithium	Male rats	↑			Peiffer <i>et al</i> , 1991
Electroconvulsive shock	Male rats		↑		Przegalinski <i>et al</i> , 1993a

↑, significant increase; ↓, significant decrease.

suggests that if GR regulation is indeed involved in the therapeutic mechanism(s) of action of antidepressants and mood stabilisers, it is not a unitary mechanism. However, a drug's ability to regulate GR number may be a good forecaster of therapeutic efficacy in patients with hypercortisolaemia.

### GR-compromised mice

With the genetic engineering technologies now available to the medical researcher it has been possible to develop a transgenic mouse line with reduced GR number. In common with patients with depression, these mice exhibit HPA disturbances and cognitive deficits which are partially normalised after antidepressant treatments (Pepin *et al*, 1992b; Montkowski *et al*, 1995). Furthermore, initial reports suggest that these transgenic mice exhibit attenuated 5-HT<sub>1A</sub>-mediated hypothermia (Man *et al*, 1999), a deficit observed in drug-free people with depression (Cowen *et al*, 1994). It is of particular note that in the study of Cowen *et al* the hypothermia was more pronounced in people with depression of melancholic type, a group strongly associated with hypercortisolaemia.

Although the evidence is less clear, there are reports that MRs (type I glucocorticoid receptors) are also susceptible to regulation by antidepressants (Seckl & Fink, 1992). These high-affinity, low-abundance receptors are extensively occupied by low, circulating levels of cortisol,

and their role in the feedback inhibition has been established (Jacobson & Sapolsky, 1991). Clearly, any modulation of MR number by antidepressants would also have important consequences for HPA activity.

### PRIMARY CONSEQUENCES OF HYPERCORTISOLAEMIA

In recent years it has become clear that, in addition to effects on metabolic and inflammatory processes, corticosteroids also play an extensive modulatory role in neurotransmission. Studies in experimental animals have indicated that expression and function of neurotransmitter receptors and enzymes, long-term potentiation and even cell survival are all influenced by corticosteroids. It is unsurprising, therefore, that behavioural indices of neurotransmitter function, such as mood and cognition, are also influenced by corticosteroid manipulations.

#### Corticosteroids and cognition

One of the most interesting findings of relevance to mood disorders is the association between hypercortisolaemia, cognitive deficits and hippocampal atrophy. Thus, it is now established that in conditions in which there are raised endogenous or exogenous corticosteroids (including Cushing's disease and severe mood disorders) there is also a significant degree of cognitive impairment (Weingartner & Silberman, 1982; Wolkowitz *et al*,

1990). In line with these clinical data, studies in experimental animals have indicated that both acute and chronic administration of glucocorticoids result in deficits in learning and memory (White-Gbadebo & Hamm, 1993; Lupien & McEwen, 1997). Chronic administration of glucocorticoids to rodents has also been shown to cause marked atrophy of neurons in the hippocampal formation, and it has been postulated that a similar neurodegenerative effect of cortisol may underlie some of the cognitive deficits observed in humans suffering from mood disorders (Sapolsky *et al*, 1986; Brown *et al*, 1999). Indeed, recent studies report that cortisol treatment induces cognitive deficits in healthy humans (Young *et al*, 1999). Furthermore, the cognitive deficits appear to be mediated in part via the frontal lobe, suggesting that this brain area may also be sensitive to the neurodegenerative effects of cortisol (Young *et al*, 1999).

In healthy volunteer subjects the cognitive deficits induced by cortisol administration are reversible, but this may not be the case with the deficits induced by hypercortisolaemia associated with mood disorders (Ferrier *et al*, 1999; Young *et al*, 1999). Thus, in unipolar and bipolar affective disorders, although cognitive deficits do show some improvement on remission of affective symptoms (paralleling the return of normal HPA function), this improvement is not complete, suggesting permanent and irreversible hypercortisolaemia-induced damage to crucial neuronal

circuits. An early re-establishment of normal HPA activity in mood disorders before permanent deficits in cognitive function occur may therefore be an important therapeutic goal.

The argument that in mood disorders, decreased GR function underlies excessive cortisol secretion and that a high cortisol level, in turn, induces deleterious effects on mood and cognition via an action on glucocorticoid receptors might appear contradictory. However, three possible explanations for the deleterious effects of high cortisol levels in the face of reduced GR function present themselves. First, elevated levels of cortisol may be sufficient to overcome the reduction in GR function and so produce an overall increase in effect. Second, it is possible that, while GRs in the hippocampus and hypothalamus associated with autoregulation of the HPA axis are reduced in function, those in other brain regions are normal. Thus, increased cortisol levels combined with normosensitive GRs might result in an increase in the (deleterious) effects of cortisol in some regions. Third, the deleterious effects of high cortisol may, in part at least, be mediated via MR (or a change in the balance of activation of MRs and GRs) or via non-receptor-mediated events.

## FUTURE THERAPEUTIC TARGETS

As discussed above, there is robust evidence of a dysfunction in HPA autoregulatory mechanisms in mood disorders, and it has been proposed that the consequent hypercortisolaemia is in some way integral to the pathogenesis of affective symptoms and cognitive deficits. It is therefore not surprising that research into potential treatments of mood disorders has focused on strategies designed to modulate the effects of hypercortisolaemia and/or the mechanisms underlying it.

### Dehydroepiandrosterone

One strategy for counteracting the effects of hypercortisolaemia, used with some success in the treatment of depression, makes use of the adrenal steroid dehydroepiandrosterone (DHEA; Bloch *et al*, 1999; Wolkowitz *et al*, 1999a). Although the physiological function of DHEA and its sulphated metabolite (DHEA-S) is unclear, these circulating corticosteroids have been shown to possess

antiglucocorticoid properties, and high cortisol/DHEA ratios are reported to be associated with persistent depression (Goodyer *et al*, 1998). However, although DHEA does possess antiglucocorticoid activity, it is partially metabolised to testosterone and oestrogen, which have mood effects of their own and may contribute to DHEA's antidepressant effect (Wolkowitz *et al*, 1999a).

### Steroid synthesis inhibitors

Raised levels of cortisol can be lowered pharmacologically by inhibitors of steroid synthesis, and drugs of this class have been used with some success in the treatment of unipolar depression. Ravaris *et al* (1988) were the first to report that daily doses of ketoconazole reduced both cortisol levels and depressive symptoms within 72 hours in a case of treatment-resistant depression. Since then there have been a number of systematic studies and case reports investigating the use of not only ketoconazole but also metyrapone and aminoglutethimide as antidepressant therapies; as yet, however, the results of these studies are inconsistent (see Murphy, 1997, for review). This inconsistency is emphasised by two recent double-blind studies. Thus, while Wolkowitz *et al* (1999b) found a marked reduction in depressive symptoms following ketoconazole treatment in patients suffering from major depression, Malison *et al* (1999) found no therapeutic effect of the drug in a similar patient group. It is worth noting that in the former study, ketoconazole was effective in hypercortisolaemic but not normocortisolaemic patients with depression (Wolkowitz *et al*, 1999b). Unfortunately, one of the main factors which limits the use of steroid biosynthesis inhibitors as antidepressive therapy is the high incidence of side-effects resulting from generalised steroid biosynthesis inhibition.

### Corticotropin-releasing hormone antagonists

On the basis of the evidence for over-secretion of CRH in mood disorders, blockade of CRH receptors has been proposed as an approach to normalising hypercortisolaemia. Preclinical studies do indeed indicate that CRH antagonists will be of use in clinical conditions related to HPA hyperactivity, particularly anxiety disorders. Clinical investigations into the use of these compounds in many psychiatric conditions are presently underway and we

await their results (see Holsboer, 1999, for review).

### Type II glucocorticoid receptor (GR) agonists

An alternative strategy for lowering circulating cortisol is activation of the GR-mediated negative-feedback mechanism that regulates cortisol levels. Sub-acute doses of dexamethasone (e.g. 3–4 mg daily for 4 days) have been reported to show antidepressant efficacy (Arana *et al*, 1995; Bodani *et al*, 1999). At this dose dexamethasone is thought not to enter the central nervous system and consequently central GRs are spared activation by this exogenous glucocorticoid. Activation of GRs at the level of the pituitary does occur, leading to a lowering of endogenous cortisol. If dexamethasone treatment does indeed act by lowering endogenous cortisol, then it would be interesting to correlate its therapeutic efficacy with the response of patients in the DST. Finally, it should be added that an advantage of the brief course of administration advocated by these studies is a reduction of the side-effects associated with longer-term dexamethasone treatment.

### Type II glucocorticoid receptor (GR) antagonists

Paradoxically, as well as GR agonists, GR antagonists have also been advocated as potentially of therapeutic benefit for mood disorders. This is based on the ability of the GR antagonist to block any detrimental effects of the raised levels of circulating cortisol and on the ability of an antagonist to up-regulate its receptor. Thus, administration of a GR antagonist might be predicted to have an acute antiglucocorticoid activity, while also causing a compensatory up-regulation of GR number, leading to enhanced negative feedback on the HPA axis. Preliminary clinical studies using the GR antagonist RU-486 (mifepristone) have been encouraging, even though some clinical efficacy may have been obscured by the prolonged administration of the drug (Murphy *et al*, 1993). However, animal work suggests that GR numbers can be increased rapidly (within hours) and it is possible that normal feedback is maintained after administration of the antagonist has ceased. This indicates that a brief (i.e. a few days) period of administration of antagonist may be adequate to increase number and normalise



HPA function. This might reduce problems of non-compliance and side-effects associated with longer-term administration (Laue *et al*, 1990). A number of new, selective GR antagonists are currently being developed, although preliminary reports suggest that some of these drugs may lack ability to up-regulate the receptors (Bachmann *et al*, 1999).

An evaluation and critique of case reports and clinical trials of some of the treatments outlined above has recently been reported (Wolkowitz & Reus, 1999). The cumulative evidence makes a strong case implicating GRs in the pathogenesis of affective disorders and suggests targeting these receptors in development of new therapies. We predict that drugs designed specifically to up-regulate GRs will be integral to future therapeutic strategies and may provide a long-awaited paradigm shift in the treatment of unipolar and bipolar mood disorders.

## REFERENCES

**Arana, G. W., Santos, A. B., Laraia, M. T., et al (1995)** Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. *American Journal of Psychiatry*, **152**, 265–267.

**Bachmann, C. G., Linthorst, A. C. E. & Reul, J. M. H. M. (1999)** Effect of chronic administration of the selective glucocorticoid receptor antagonists ORG 34850, ORG 34116, and ORG 34517 on the rat hypothalamic–pituitary–adrenocortical axis. *European Neuropsychopharmacology*, **9**, P1.102.

**Bloch, M., Schmidt, P. J., Danaceau, M. A., et al (1999)** Dehydroepiandrosterone treatment of midlife dysthymia. *Biological Psychiatry*, **45**, 1533–1541.

**Bodani, M., Sheehan, B. & Philpot, M. (1999)** The use of dexamethasone in elderly patients with antidepressant-resistant depressive illness. *Journal of Psychopharmacology*, **13**, 196–197.

**Brown, E. S., Rush, A. J. & McEwen, B. S. (1999)** Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. *Neuropsychopharmacology*, **21**, 474–484.

**Cowen, P. J., Power, A. C., Ware, C. J., et al (1994)** 5-HT<sub>1A</sub> receptor sensitivity in major depression. A neuroendocrine study with buspirone. *British Journal of Psychiatry*, **164**, 372–379.

**Deuschle, M., Schweiger, U., Weber, B., et al (1997)** Diurnal activity and pulsatility of the hypothalamus–pituitary–adrenal system in male depressed patients and healthy controls. *Journal of Clinical Endocrinology and Metabolism*, **82**, 234–238.

**Ferrier, I. N., Stanton, B. R., Kelly, T. P., et al (1999)** Neuropsychological function in euthymic patients with bipolar disorder. *British Journal of Psychiatry*, **175**, 246–251.

**Freud, S. (1905)** *Three essays on the theory of sexuality*. Reprinted (1953–1974) in the *Standard Edition of the Complete Psychological Works of Sigmund Freud* (trans. and ed. J. Strachey), vol. 3. London: Hogarth Press.

## CLINICAL IMPLICATIONS

- Hypothalamic–pituitary–adrenal axis function is abnormal in mood disorders.
- The type II glucocorticoid receptor subtype (GR) can be modulated by antidepressants and mood stabilisers.
- Direct antagonism of GRs may be a future therapeutic strategy in the treatment of mood disorders.

## LIMITATIONS

- We have selectively reviewed a complex area of neuroendocrinology.
- Evidence that antidepressants and mood stabilisers modulate GRs is mainly taken from animal studies and there is little direct evidence of such a modulation in humans.
- GR antagonists have not yet been categorically shown to be effective in the treatment of mood disorders.

RICHARD McQUADE, DPhil, Senior Research Associate, ALLAN H. Y. YOUNG, MRCPsych, Professor of Psychiatry, The Stanley European Bipolar Research Centre, Psychiatry Research Laboratory, The Medical School, Newcastle upon Tyne, UK

Correspondence: Professor A. H. Young, The Stanley European Bipolar Research Centre, Psychiatry Research Laboratory, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4H. Tel. /fax: 0191 222 8210; e-mail: a.h.young@ncl.ac.uk

(First received 6 December 1999, final revision 20 April 2000, accepted 10 May 2000)

**Gibbons, J. L. (1964)** Cortisol secretion rate in depressive illness. *Archives of General Psychiatry*, **10**, 572–575.

**Goodyer, I. M., Herbert, J. & Altham, P. M. (1998)** Adrenal steroid secretion and major depression in 8- to 16-year-olds, III. Influence of cortisol/DHEA ratio at presentation on subsequent rates of disappointing life events and persistent major depression. *Psychological Medicine*, **28**, 265–273.

**Heuser, I., Yassouridis, A. & Holsboer, F. (1994)** The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *Journal of Psychiatric Research*, **28**, 341–356.

**Holsboer, F. (1999)** The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. *Journal of Psychiatric Research*, **33**, 181–214.

**— & Barden, N. (1996)** Antidepressants and hypothalamic–pituitary–adrenocortical regulation. *Endocrine Reviews*, **17**, 187–205.

**Jacobson, L. & Sapolsky, R. (1991)** The role of the hippocampus in feedback regulation of the hypothalamic–pituitary–adrenocortical axis. *Endocrine Reviews*, **12**, 118–134.

**Jones, M. T., Gillham, B., Campbell, E. A., et al (1987)** Pharmacology of neural pathways affecting CRH secretion. *Annals of the New York Academy of Sciences*, **512**, 162–175.

**Kraepelin, E. (1896)** *Psychiatrie* (5th edn). Leipzig: Barth.

**Laue, L., Lotze, M. T., Chrousos, G. P., et al (1990)** Effect of chronic treatment with the glucocorticoid antagonist RU 486 in man: toxicity, immunological, and hormonal aspects. *Journal of Clinical Endocrinology and Metabolism*, **71**, 1474–1480.

**Lupien, S. J. & McEwen, B. S. (1997)** The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Research Reviews*, **24**, 1–27.

**Malison, R. T., Anand, A., Pelton, G. H., et al (1999)** Limited efficacy of ketoconazole in treatment-refractory major depression. *Journal of Clinical Psychopharmacology*, **19**, 466–470.

**Man, M. S., McAllister-Williams, R. H., Steckler, T., et al (1999)** 5-HT<sub>1A</sub> receptor function in GR transgenic mice. *Journal of Psychopharmacology*, **13** (suppl. A), A32.

**Michael, R. P. & Gibbons, J. L. (1963)** Interrelationships between the endocrine system and neuropsychiatry. *International Review of Neurobiology*, **5**, 243–302.

**Montkowski, A., Barden, N., Wotjak, C., et al (1995)** Long-term antidepressant treatment reduces behavioural deficits in transgenic mice with impaired glucocorticoid receptor function. *Journal of Neuroendocrinology*, **7**, 841–845.

**Murphy, B. E. (1997)** Antiglucocorticoid therapies in major depression: a review. *Psychoneuroendocrinology*, **22** (suppl. 1), S125–S132.

**—, Filipini, D. & Ghadirian, A. M. (1993)** Possible use of glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU 486. *Journal of Psychiatry and Neuroscience*, **18**, 209–213.

- Nemeroff, C. B., Widerlov, E., Bissette, G., et al (1984)** Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*, **226**, 1342–1344.
- Owens, M. J. & Nemeroff, C. B. (1993)** *The Role of CRF in the Pathophysiology of Affective Disorders: Laboratory and Clinical Studies* (vol. 172). New York: John Wiley & Sons.
- Pariante, C. M., Pearce, B. D., Pisell, T. L., et al (1997)** Steroid-independent translocation of the glucocorticoid receptor by the antidepressant desipramine. *Molecular Pharmacology*, **52**, 571–581.
- Peiffer, A., Veilleux, S. & Barden, N. (1991)** Antidepressant and other centrally acting drugs regulate glucocorticoid receptor messenger RNA levels in rat brain. *Psychoneuroendocrinology*, **16**, 505–515.
- Pepin, M. C., Beaulieu, S. & Barden, N. (1989)** Antidepressants regulate glucocorticoid receptor messenger RNA concentrations in primary neuronal cultures. *Brain Research. Molecular Brain Research*, **6**, 77–83.
- , **Govindan, M. V. & Barden, N. (1992a)** Increased glucocorticoid receptor gene promoter activity after antidepressant treatment. *Molecular Pharmacology*, **41**, 1016–1022.
- , **Pothier, F. & Barden, N. (1992b)** Antidepressant drug action in a transgenic mouse model of the endocrine changes seen in depression. *Molecular Pharmacology*, **42**, 991–995.
- Przegalinski, E., Budziszewska, B., Siwanowicz, J., et al (1993a)** The effect of repeated combined treatment with nifedipine and antidepressant drugs or electroconvulsive shock on the hippocampal corticosteroid receptors in rats. *Neuropharmacology*, **32**, 1397–1400.
- & — (1993b) The effect of long-term treatment with antidepressant drugs on the hippocampal mineralocorticoid and glucocorticoid receptors in rats. *Neuroscience Letters*, **161**, 215–218.
- Ravaris, C. L., Sateia, M. J., Beroza, K. W., et al (1988)** Effect of ketoconazole on a hypophysectomized, hypercortisolemic, psychotically depressed woman. *Archives of General Psychiatry*, **45**, 966–967.
- Raven, P. W., O'Dwyer, A. M., Taylor, N. F., et al (1996)** The relationship between the effects of metyrapone treatment of depressed mood and urinary steroid profiles. *Psychoneuroendocrinology*, **21**, 277–286.
- Reul, J. M., Stec, I., Soder, M., et al (1993)** Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic–pituitary–adrenocortical system. *Endocrinology*, **133**, 312–320.
- Rossby, S. P., Nalepa, I., Huang, M., et al (1995)** Norepinephrine-independent regulation of GR11 mRNA in vivo by a tricyclic antidepressant. *Brain Research*, **687**, 79–82.
- Sapolsky, R. M., Krey, L. C. & McEwen, B. S. (1986)** The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews*, **7**, 284–301.
- Seckl, J. R. & Fink, G. (1992)** Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus in vivo. *Neuroendocrinology*, **55**, 621–626.
- Swann, A. C., Stokes, P. E., Casper, R., et al (1992)** Hypothalamic–pituitary–adrenocortical function in mixed and pure mania. *Acta Psychiatrica Scandinavica*, **85**, 270–274.
- Webster, M. J., O'Grady, J. O., Orthmann, C., et al (1999)** Decreased glucocorticoid receptor mRNA levels in individuals with depression, bipolar disorder and schizophrenia. *Schizophrenia Research*, **41**, 111.
- Weingartner, H. & Silberman, E. (1982)** Models of cognitive impairment: cognitive changes in depression. *Psychopharmacology Bulletin*, **18**, 27–42.
- White-Gbadebo, D. & Hamm, R. J. (1993)** Chronic corticosterone treatment potentiates deficits following traumatic brain injury in rats: implications for aging. *Journal of Neurotrauma*, **10**, 297–306.
- Wolkowitz, O. M., Reus, V. I., Weingartner, H., et al (1990)** Cognitive effects of corticosteroids. *American Journal of Psychiatry*, **147**, 1297–1303.
- & — (1999) Treatment of depression with antiglucocorticoid drugs. *Psychosomatic Medicine*, **61**, 698–711.
- , —, **Keebler, A., et al (1999a)** Double-blind treatment of major depression with dehydroepiandrosterone. *American Journal of Psychiatry*, **156**, 646–649.
- , —, **Chan, T., et al (1999b)** Antiglucocorticoid treatment of depression: double-blind ketoconazole. *Biological Psychiatry*, **45**, 1070–1074.
- Young, A. H., Sahakian, B. J., Robbins, T. W., et al (1999)** The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology (Berlin)*, **145**, 260–266.
- Zhou, D. F., Shen, Y. C., Shu, L. N., et al (1987)** Dexamethasone suppression test and urinary MHPG X SO<sub>4</sub> determination in depressive disorders. *Biological Psychiatry*, **22**, 883–891.
- Zobel, A. W., Yassouridis, A., Frieboes, R. M., et al (1999)** Prediction of medium-term outcome by cortisol response to the combined dexamethasone–CRH test in patients with remitted depression. *American Journal of Psychiatry*, **156**, 949–951.