

The neuroendocrinology of depression and chronic stress

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This chapter will review basic and clinical studies of the social, genetic and developmental influences upon the reactivity of the hypothalamic pituitary adrenal (HPA) axis and the relationship of these to depression. Significant advances have taken place in each of these areas and it is now possible to interlink many of these areas of work. In order to do so, this chapter will be organised into five sections. The first section will show how the neuroendocrinology of chronic stress is characterised by an up-regulation of the central drive to the HPA axis in conjunction with down-regulation of its negative feedback control. The second will show that very similar processes occur in depressive illness. The third section will describe social, developmental and genetic influences on the HPA axis both in experimental animals and in man. The fourth will show how activation of the HPA axis can influence the development of animal models of depression as well as the onset and perpetuation of clinical depression. The final section will draw together an overall hypothesis and indicate the potential for new treatments for depression that arise from this work.

The neuroendocrinology of acute and chronic stress

The secretion of corticosteroid hormones (predominantly cortisol in man and corticosterone in the rat) is the most important endocrine component of the response to stress and the one that is most necessary for successful adaptation: the acute response has a time course of 1–2 h and the chronic response one of days or weeks.

HPA activation in response to acute stress – animal studies

The *central drive* to the stress response of the HPA axis is organised by the parvocellular component of the paraventricular nucleus (PVN) of the hypothalamus. Some of these cells synthesise corticotropin releasing hormone (CRH) alone and some both CRH and arginine vasopressin (AVP), but both types of cells project to the external zone of the median eminence and release their hormones into the hypophyseal portal system which carries the hormones to the anterior pituitary gland. In response to an acute stress there is an increase in the synthesis of CRH mRNA and

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AVP mRNA in parvocellular cells in the PVN¹, an increase in CRH and AVP message in the median eminence and an increased release of CRH and AVP into portal blood. CRH and AVP act synergistically at the pituitary to stimulate the release of adrenocorticotrophic hormone (ACTH). In animals, though not necessarily in man, oxytocin and other peptides act synergistically with CRH to stimulate the release of ACTH from the pituitary. In animals and also in man, a recently described hormone, atrial natriuretic hormone (ANH) acts at the pituitary to inhibit the secretion of ACTH². ACTH in turn acts at the adrenal glands both to stimulate the synthesis and release of corticosteroids and also to stimulate growth of adrenocortical cells.

Negative feedback control of the HPA response to stress is exerted by corticosteroids at all the above levels but with a different time course at different levels. As plasma corticosteroid concentrations are rising, corticosteroid receptors in the hippocampus are activated in order to mediate *fast feedback* inhibition of the HPA axis. Fast feedback operates over a time scale of minutes and is proportional to the rate of change in plasma corticosteroids³. Lesions to the hippocampus or to its projections to the PVN result in impairment of fast feedback and consequently in prolongation of the stress response^{4,5}. Fast feedback can be investigated in man by measurement of the suppression of ACTH and/or β endorphin following an infusion of hydrocortisone⁶. *Delayed feedback*, in contrast, takes place over a time scale of hours and is proportional to the mean plasma corticosteroid concentration over that time, and not to the rate of its change: it is seen in the presence of pathologically high corticosteroid concentrations or following treatment with synthetic glucocorticoids such as dexamethasone. Delayed feedback can be tested in clinical practice by the suppression of HPA function following dexamethasone treatment, a test which involves glucocorticoid receptors in the pituitary⁷.

HPA activation in response to acute stress – human studies

The time course of the human ACTH and corticosteroid response to stress⁸ is similar to that which is seen in experimental animals and there is no reason to doubt that similar mechanisms operate in animals and in man.

HPA activation in response to chronic stress – animal studies

In the presence of chronic stress it is necessary to maintain an increased secretion of corticosteroid hormones despite negative feedback control,

and to mount an additional corticosteroid response to superimposed chronic stress⁹. This is achieved as a result of adaptive changes at three levels of the HPA axis. In almost every model which has been investigated a consistent *increase in the central drive* has been reported as shown by an increased expression of CRF mRNA and/or AVP mRNA in parvocellular cells in the PVN or in their terminals in the median eminence^{4,10-14}.

In most of the chronic stress paradigms to have been investigated, a down-regulation has been reported in the corticosteroid receptors which mediate negative feedback regulation of the HPA axis¹⁵. Corticosteroid hormones act as two classes of receptors—the mineralocorticoid receptors (MRs) which have high affinity for corticosteroids, and so are fully occupied for most of the day, and the glucocorticoid receptors (GRs), which have low affinity for corticosteroids and which are thought to become activated in response to stress and to be important in terminating the stress response¹⁶. In response to chronic stress, a *reduction in both GR and MR numbers*¹⁴ has been reported particularly in the hippocampus (the site of the 'fast feedback' inhibition)^{14,17}. Chronic treatment with ECS is an exception but although hippocampal corticosteroid receptors are not down-regulated, CRH mRNA is increased as is adrenal volume and the net effect is an increase both in basal corticosteroid secretion and the corticosteroid response to ECS¹⁸. Both 'fast' and 'delayed' feedback inhibition are impaired in animals exposed to chronic stress¹⁹. A third adaptation to chronic stress is *hypertrophy of the adrenal glands* which again is reported after most of the above forms of chronic stress^{14,20}.

The importance of this description of the neuroendocrinology of chronic stress in animals is that each of these three processes can be investigated in clinical depression.

The neuroendocrinology of depression

As far as the HPA axis is concerned, the principal change in depression is an increased secretion of cortisol throughout the 24 h. This change is seen in approximately 50% of patients with major depression²¹⁻²³. The underlying mechanisms appear to be very similar to those which have been described following chronic stress in animals.

It is only possible to study the effects of depression on the central drive of the HPA axis at a molecular level in *post mortem* tissue of depressive suicides when there are inevitable artefacts caused by the means of suicide. Nonetheless, the findings are similar to those that are seen in

animals exposed to chronic stress. In one small but highly informative study, the brains of 6 depressed suicides have been shown to have a 4-fold increase in the number of CRH expressing cells in the PVN and a 3-fold increase in the co-expression of CRH and AVP in the PVN²⁴. These findings match those reported above in studies of the effect of chronic stress on the HPA axis in experimental animals. Other evidence for an increased central drive includes reports that in depression the HPA axis over-rides the effects of cortisol synthesis inhibition for example by metyrapone^{25,26}. Whether the increased central drive of the HPA axis in depression is mediated by CRH and/or by AVP is not known. Reports of a reduced ACTH response to CRH in depression^{27,28} were once thought to indicate an increased release of CRH into postal blood: however, it is now known that the ACTH response to CRH in depression becomes normal if plasma cortisol is normalised by pre-treatment with metyrapone^{29,30}. There is some evidence of a generalised activation of CRH neurones in depressed patients resulting in increased CSF concentrations of CRH^{31,32} and possibly in reduced numbers of CRH receptors in the frontal cortex of depressed suicides^{33,34}, but there is no direct evidence for an increased release of CRH into the hypophyseal portal system. The increased central drive to the HPA axis in depression could therefore be mediated either by CRH or by AVP or by both.

In depressed patients as in chronically stressed animals there is also *impaired negative feedback* control of the HPA axis by corticosteroids. The dexamethasone test is a test of delayed negative feedback at GRs within the pituitary and the DST is clearly abnormal in many patients with melancholia^{35,36}, although also in patients with some other psychiatric diagnoses³⁷. The inhibition of ACTH/ β endorphin in response to an infusion of hydrocortisone is a test of fast feedback inhibition at the hippocampus and this also is impaired in depression³⁸.

The third type of HPA adaptation to chronic stress to be reported in experimental animals has also been described in depressed patients. *Hypertrophy of the adrenal gland* in depressed patients has been demonstrated by CT³⁹, by MRI⁴⁰ and at *post mortem*⁴¹. An enlargement of pituitary gland volume in depression has also been demonstrated⁴².

In summary, the HPA axis of the hypercortisolaemic depressed patient shares three characteristics with that of the chronically stressed rat: in both there is an increased central drive, an impaired negative feedback and hypertrophy of the adrenal gland (Table 1). As a result, the hypercortisolaemic depressed patient, like the chronically stressed rat, is able to sustain an increased secretion of corticosteroid hormones and to mount an additional corticosterone response to superimposed stress, despite the existence of negative feedback control.

Table 1 Common effects of chronic stress in animals and depressive illness in man on regulation of the HPA axis

	Animal models of chronic stress	Depressive illness
Evidence for increased central drive to HPA axis	Herman <i>et al.</i> 1989 ⁴ Angulo <i>et al.</i> 1991 ¹⁰ de Goeij <i>et al.</i> 1992 ¹¹ Bartanusz <i>et al.</i> 1993 ¹² Harbuz <i>et al.</i> 1993 ¹³	Roadsbeer <i>et al.</i> 1994 ²⁴ Ur <i>et al.</i> 1992 ²⁵ Young <i>et al.</i> 1994 ²⁶
Evidence of impaired negative feedback	Sapolsky <i>et al.</i> 1984 ¹⁵ Young <i>et al.</i> 1990 ^{18,19}	Carroll <i>et al.</i> 1981 ³⁴ Young <i>et al.</i> 1991 ³⁸
Evidence of adrenal hypertrophy	Herman <i>et al.</i> 1995 ¹⁴	Dorovini-Zis & Zis 1987 ⁴¹ Nemeroff <i>et al.</i> 1992 ³⁹ Rubin <i>et al.</i> 1995 ⁴⁰

Neuroendocrine aspects of the environmental and genetic causes of depression

Depressive illness results from an interaction between the effects of environmental stress and genetic predisposition. For the commonest types of depression, the influence of environmental stress is greater than that of genetic predisposition⁴³ and the genetic influence may also effect some of the environmental measures⁴⁴.

Environmental stress falls into three main categories

1. Provoking agents are environmental changes which precede and increase the likelihood of subsequent illness. A life event is a provoking agent the onset of which can be precisely timed (e.g. a bereavement) in contrast to a long standing 'chronic difficulty' (e.g. marital discord)⁴⁵.
2. Vulnerability factors are the second class of environmental influence on depression and can be defined as psychosocial influences which increase the likelihood that a given life-event or chronic difficulty will be followed by a depression. Child abuse is such a vulnerability factor: social support is another⁴⁶.
3. Risk factors are the third type of environmental cause of depression. A risk factor is a psychosocial measure which is associated with an increased risk of depression but for which no interaction has been demonstrated with the effects of life-events and chronic difficulties. Neuroticism is such a risk factor⁴⁷.

The *genetic* influence on the onset of depression can be mediated either directly or indirectly through the genetic influence on personality and life events⁴⁸.

In this section, the evidence will be reviewed that the secretion of cortisol is a biological marker of these influences on depression. The next section will suggest that cortisol may also be a mediator of some of these effects.

Neuroendocrine studies of life-events and chronic difficulties – animal studies

Within the animal kingdom, social hierarchy provides a context within which it is possible to study social processes which are analogous to chronic difficulties and life events. In the well described case of the wild olive backed baboon⁴⁹, the dominant male baboons have preferential access to mates and places of safety in the event of an attack by predators: subordinate baboons lack both and in addition suffer from receiving the displaced aggression from frustrated baboons higher up in the hierarchy. In the clinical context such a situation of social subordination would be classified as a 'chronic difficulty' and it is, therefore, of interest that almost universally throughout the animal kingdom low social hierarchy is associated with a sustained activation of the HPA axis. This has been studied in particular detail in the subordinate olive backed baboon in which hypercortisolaemia has been associated with many of the neuroendocrine changes that are seen in depression including dexamethasone resistance^{50,51} and reduced ACTH responses to CRH⁵². Loss of social rank within such a social system would accord in the clinical context to a severely threatening life event and it is, therefore, intriguing to note that loss of social rank⁵³, and even threat to loss of social rank⁵⁴, have been reported to be associated with increased activity of the HPA axis.

Neuroendocrine studies of life-events – human studies

To date, there have been only three clinical studies of the effects of life-events and/or chronic difficulties on the HPA axis and in all three cases a sustained activation of the HPA axis has been reported. The first was a longitudinal study of healthy elderly men and women in whom plasma cortisol was measured on two occasions 1 year apart. The volunteers were asked to report the occurrence of severely threatening life-events over the intervening year and a third plasma cortisol sample was taken within 3 months of the onset of the event. Raised plasma cortisol concentrations were found in plasma taken from healthy volunteers who had experienced threatening life events⁵⁵. The fact that plasma cortisol

concentrations were raised up to 3 months after the onset of a severely threatening life-event implies a resetting of the control of the HPA axis and not just a stress response. Similar conclusions can be drawn from the report that depressed patients with recent history of life-events and chronic difficulties excrete more cortisol⁵⁶ and have higher plasma cortisol concentrations⁵⁷ than matched depressed patients without life-events and chronic difficulties.

Neuroendocrine studies of early adversity – animal studies

A variety of aversive experiences *in utero* or in the neonatal period have been shown to have enduring effects upon emotional and neuroendocrine reactivity in later life. Several of these effects can be reversed by the experimental procedures of ‘handling’ and ‘adoption’ which result in increased maternal attention.

Thus rats exposed to noise or light *in utero* develop a fearful temperament in later life as shown by reduced activity in a novel situation, an enhanced corticosteroid response to the novel situation, and enhanced punishment induced suppression of an appetitive response⁵⁸. Similar behaviours are seen in the offspring of pregnant rats exposed to the stress of immobilisation and in these animals a prolonged corticosteroid response to stress could be correlated with down-regulation of hippocampal corticosteroid receptors⁵⁹: all of these effects were reversed by ‘adopting’ the offspring—a procedure which resulted in increased attention from the new mother. Endotoxic shock *in utero* also results in desensitisation of hippocampal GRs and consequent prolongation of the corticosterone response to stress: increased concentrations of AVP and CRH in median eminence were found suggesting an increased central drive of the HPA axis⁶⁰. Maternal separation during early postnatal life also results in increased corticosterone responses to stress and increased expression of CRH mRNA in the PVN⁶¹.

The opposite effect is produced by the ‘handling’ of young rats by laboratory staff. Fearful behaviour is suppressed^{62,63}, GRs in the hippocampus are up-regulated⁶⁴ and the corticosteroid response to stress is terminated more rapidly than before handling⁶⁵.

In summary, several aversive experiences both *in utero* and in the neonatal period result in a sensitisation of the emotional and HPA responses to subsequent stress, whereas the more pleasant experiences of ‘handling’ and ‘adoption’ have the opposite effect. In the case of handling, this effect persists throughout the life cycle and in animals influences age related cognitive decline⁶⁶.

Neuroendocrine studies of the effects of childhood adversity – clinical studies

To date, only one study has reported the effects of childhood abuse on HPA function. Reduced ACTH responses to CRH with normal 24 h excretions of urinary free cortisol have been reported in 13 children aged 7–15 years who had experienced prior sexual or physical abuse⁶⁷. These findings which need follow-up could be explained by a stress induced down-regulation of pituitary CRH receptors with normal negative feedback control of cortisol excretion. They suggest that, in humans, early traumatic experience can have long lasting effects upon the stress response.

Effects of social support on the HPA response to stress – animal studies

In squirrel monkeys, membership of a same-sex social group results in an attenuated corticosteroid response to stress when compared with the response of isolated monkeys⁶⁸.

A comparable stress-buffering effect of social support has been demonstrated in human infants aged 9 months. The cortisol response to a novel (hospital Out Patient) setting is reduced if the infant is accompanied by a care-giver who interacts positively with the infant⁶⁹ as compared with a non interactive care-giver.

Genetic influence on the HPA response to stress – animal studies

A genetic influence on the HPA response to stress has been demonstrated by selective breeding experiments. Animals bred selectively for a behavioural characteristic have in several cases shown an altered HPA response to stress as well⁷⁰. In some of these strains, responsiveness of the HPA and emotional reactivity have been found to co-vary.

The *LEW/N* strain of Lewis rats which have been bred for sensitivity to streptococcal induced arthritis have reduced HPA responses to stress⁷¹, which explains their susceptibility to experimentally induced arthritis.

Roman Low Avoidance (RLA) rats have been selectively bred for low acquisition of a two-way conditioned avoidance response in the shuttle box⁷². RLA strains show fearful behaviour generally and, for example, they display little spontaneous activity in a novel ('open field') environment⁷³ when compared to Roman High Avoidance (RHA) rats which were bred for speed of acquisition of conditioned avoidance. Compared with RHA, the RLA strains generally show increased HPA

responses to stress⁷⁴⁻⁷⁶. However, the relationship is not invariable and in RLA rats the association between emotional reactivity and HPA reactivity is seen in adult but not in juvenile rats⁷⁵.

Maudsley Reactive rats which were bred for an autonomic measure of emotional reactivity (defaecation when placed in an unfamiliar environment) also show evidence of emotional reactivity on other tests⁷⁷. Maudsley Reactive rats have also been reported to have enhanced HPA responses to stress in some⁷⁸, but not all⁷⁹, reports.

Chinese Meishan pigs which have been selectively bred for agricultural purposes have overactive HPA axes when compared with European large white pigs. Compared to European large whites, the Chinese Meishan pig has higher basal corticosteroid and higher corticosteroid responses to a novel situation and also behavioural evidence of increased fearfulness (reduced locomotion) in the novel environment. However, no association between emotional and neuroendocrine reactivity was evident in the offspring of Chinese Meishan and European large white pigs⁸⁰. Thus, although both neuroendocrine and emotional reactivity are subject to genetic influence, the association between the two is not genetically determined at least in these strains of pigs.

Genetic influences on the HPA axis – clinical studies

Clinical studies of the genetic influence on the HPA response to stress have been strikingly neglected. There have been three twin studies which have clearly demonstrated that in man, as in animals, the secretion of corticosteroids is under genetic control⁸¹⁻⁸³, but no large scale systematic attempts have been made to measure the heritability of the cortisol response to acute and chronic stress in man. It is possible that the unexplained variation in plasma cortisol in depression may be due to genetic factors and it is possible that individual differences in the HPA response to stress may predict individual differences in susceptibility to depression and to other stress related disorders.

Emotional reactivity and reactivity of the HPA axis – animal studies

Animal studies have been reviewed which demonstrate separate genetic influences both on emotional reactivity and reactivity of the HPA axis (see above). Studies of the early environment have been reviewed in which aversive early experience increases measures of emotional and neuroendocrine reactivity in later life whereas 'adoption' has the opposite effect (see above). The importance of emotional reactivity for the present

review is that the human equivalent, neuroticism, is a precursor of depression.

Emotional reactivity (neuroticism) and reactivity of the HPA axis – human studies

The temperament of infants studied in the fourth month of life has been categorised in a way that is similar to that in which emotional reactivity has been categorised in experimental animals. The behaviour of infants has been observed in an unfamiliar and stressful laboratory ('open field') situation. 'Low reactive' children in the novel situation show relatively little crying or other motor behaviour whereas 'high reactive' infants show more evidence of showing distress. When re-tested at 14 months of age (at which age anxiety can be rated by an observer) the formerly 'low-reactive' infant show high levels of anxiety in an unfamiliar situation whereas the 'high reactive' infant in general showed lower levels of anxiety. The characteristics of 'low reactive' or 'inhibited' behaviour has been shown in a twin study to be a heritable characteristic⁸⁴. The salivary secretion of cortisol has been measured both in familiar (home) and unfamiliar (clinic) situations in these children at the age of 5.5 years and 'low reactive' or 'inhibited' children have been found to have higher salivary cortisol concentrations than control children⁸⁵. These findings are closely comparable to the animal studies in which animals bred for high levels of emotional reactivity have enhanced HPA responses to a novel ('open field') environment.

We have recently found that, during pregnancy, plasma concentrations of cortisol are influenced by neuroticism although at other points in the adult life cycle this is not the case (Checkley *et al*, unpublished data). However, the closely related measure of 'behavioural inhibition' did weakly correlate with plasma cortisol in a sample of 4462 male US veterans⁸⁶. Further studies are needed, but there is some evidence that neuroticism, which is a risk factor for the development of depression, can under some circumstances be associated with hypercortisolaemia.

Neuroendocrine consequences of the environmental causes of depression – conclusions

It is a remarkable fact that the environmental influences which social scientists have found to have the greatest influence on the onset and course of depression are the same psychological influences with the greatest effect on the secretion of corticosteroids in animals. Though

studied in much less detail in humans, the available data suggest that these same influences—life events, chronic difficulties and childhood abuse, for example—lead to a sustained activation of the HPA axis in man (Table 2). At the very least, these findings point to the secretion of cortisol as a biological marker of the central effect of the psychosocial causes of depression. The next section of this review will consider the evidence that the secretion of cortisol is not only a marker of the psychosocial influence upon depression but that it may also be a mediator.

Table 2 Effects upon the HPA axis of environmental influences which have been shown to influence the course of depressive illness

Clinical studies			Animal studies	
Provoking agent	Life events	Willis <i>et al.</i> 1987 ^{55*}	Loss of hierarchy	Jones <i>et al.</i> 1995 ^{53*}
	Chronic difficulties	Calloway & Dolan 1989 ^{54*}	Low social rank	Sapolsky 1990 ^{54*}
Vulnerability factor	Childhood abuse	de Bellis <i>et al.</i> 1994 ^{47*}	Maternal separation	Plotsky & Meaney 1993 ^{61*}
Protective factor	Social support	Gunnar <i>et al.</i> 1992 ^{69**}	'Social support'	Lyons & Levine 1994 ^{64**}
			'Adoption'	Maccari <i>et al.</i> 1995 ^{59**}
			'Handling'	Meaney <i>et al.</i> 1989 ^{64**}
Risk factors	Neuroticism	Checkley <i>et al.</i> , unpublished*	Emotional reactivity	Castanon <i>et al.</i> 1994 ^{75*}
				Gentsch <i>et al.</i> 1988 ^{78*}
				Mormede <i>et al.</i> 1994 ^{80*}

*Indicates activation of HPA axis activity and ** indicates inhibition. For further details see text

HPA activation and the onset and maintenance of depression

The causal relationship between corticosteroids and depression can be studied: (i) in animal models of depression; (ii) in Cushing's syndrome; and (iii) by treating depressed patients with drugs which effect corticosteroids.

Animal studies

The 'swim test' has been developed as a simple behavioural model of depression and, as such, it has been extremely successful in the screening for the antidepressant efficacy of new drugs⁸⁷. Rats are placed in a cylinder of water for 15 min and when they learn that escape is impossible they adopt a passive posture with the snout just above the water. When re-tested in the cylinder 24 h later, rats adopt the immobile position quicker. Antidepressant drugs reduce the development of immobility on retesting⁸⁷. Immobility does not develop in adrenalecto-

mised rats unless synthetic or natural steroids are administered. It is the glucocorticoid receptor (GR) which is involved, since the effect of adrenalectomy can be reversed by dexamethasone, which has high affinity for GRs but low affinity for MRs. Furthermore, the ability of dexamethasone to reverse the effect of adrenalectomy can be prevented by re-treatment with the selective GR antagonist RU 38486. Finally, and most interestingly, of all the GR antagonist RU 38486 prevents the development of immobility when injected directly into the dentate gyrus of the hippocampus⁸⁸.

Exactly the same procedure also influences the expression of a completely different animal model of depression. The 'learned helplessness' paradigm involves a 40 min period of exposure to uncontrollable electric shock and then, 1 day later, a similar exposure to shocks which can be terminated by pressing a lever. Animals which do not learn to press the lever within 10 tries are deemed to show 'learned helplessness'. The 'learned helplessness' animal yields abnormal dexamethasone test results⁸⁹, presumably because of a central activation of the HPA axis. Following adrenalectomy, a much greater proportion of animals show the features of 'learned helplessness', the effect of adrenalectomy being reversed by hydrocortisone⁹⁰. The effect of corticosteroids on learned helplessness involves the activation of GRs in the dentate gyrus of the hippocampus since infusion of the selective GR antagonist RU 38486 provokes the expression of 'learned helplessness'⁹¹. It is not known why the same GR antagonist should have opposite effects on two different models of depression following infusion into the same part of the hippocampus, but both experiments point to the importance of hippocampal GRs in animal models of depression.

A third animal model of depression emphasises the link between 5HT_{1A} receptors, corticosteroids and stress. The behavioural consequences of social hierarchies in rodents are enhanced when rats are housed in 'visible burrow systems'. Socially submissive rats have a sustained activation of the HPA axis under these conditions and when tested in an open field some submissive rats have enhanced corticosteroid responses to experimental stress. The rats with enhanced HPA responses to experimental stress also have down-regulation of 5HT_{1A} receptors in the hippocampus and these same rats when studied in the visible burrow system are the least active behaviourally⁹². The parallels between these changes and the changes seen in animal models of depression are striking and it is of particular interest that the glucocorticoid receptors (GRs) are co-localised with 5HT_{1A} receptors within the hippocampus and that the activation of these GRs is critical for the development of several animal models of depression.

Taken together, these and other models⁹³ suggest that the effects of environmental stress on animal models of depression are mediated by the action of corticosteroids at the central glucocorticoid receptors (GRs) in

the dentate gyrus with a subsequent down-regulation of 5HT_{1A} receptors in the same cells.

Cushing's syndrome

It has long been known that depression is seen in patients with Cushing's syndrome⁹⁴, although it was some time before this was demonstrated in a controlled study using standardised psychiatric diagnoses⁹⁵. Cushing's syndrome can result either from a pituitary or ectopic tumour which secretes ACTH (and hence increases the secretion of cortisol) or it can be caused by an adrenal tumour which secretes excessive amounts of cortisol (and hence suppresses the secretion of ACTH). The fact that depression is seen in 50% of both types of Cushing's syndrome indicates that it is the cortisol which causes the depression rather than ACTH or related pituitary peptides. This conclusion is supported by the fact that metyrapone (which blocks the synthesis of cortisol and causes a compensatory increase in the secretion of ACTH) successfully treats the depression that is secondary to Cushing's syndrome⁹⁶.

Antidepressant effects of drugs which influence corticosteroids

The degree of hypercortisolaemia which is seen in patients with Cushing's syndrome overlaps with that which is seen in depression and so if the depression that is associated with Cushing's syndrome can be treated by inhibiting the synthesis of cortisol then it follows that primary depressive illness may also be treatable by inhibiting the synthesis of cortisol. To date, there is one placebo controlled study which has reported an antidepressant effect of metyrapone⁹⁷ and several uncontrolled reports⁹⁸⁻¹⁰¹. There is also one report that a bolus injection of hydrocortisone may have an antidepressant effect¹⁰², as may 4 days of treatment with dexamethasone¹⁰³. The apparent discrepancy between the antidepressant efficacy of cortisol synthesis inhibitors on the one hand, and of glucocorticoids on the other, may be explained by their differential effects upon GRs and MRs. GRs will be activated both by dexamethasone treatment and by high doses of hydrocortisone, whereas inhibiting the synthesis of cortisol will influence MR function. It will be important to test the antidepressant efficacy of MR as well as GR antagonists when these become available for use in man.

In conclusion, there is excellent evidence that corticosteroids mediate the effects of chronic stress on the development of animal models of depression and there is good evidence that in man cortisol mediates the

influence of Cushing's syndrome on depression. There is preliminary evidence that in primary depressive illness hypercortisolaemia perpetuates depressive disorder. Whether or not cortisol mediates the effects of environmental stress on depression is not known and no direct test of this possibility has been reported.

Finally it is important to note that entrapment, humiliation and loss which are the determining characteristics of the stressors which provoke depression in man¹⁰⁴ are also characteristics of the stressors which provoke animal models of depression (Table 3).

Table 3 This shows for each of four animal models of depression the involvement of the hypothalamic pituitary adrenal (HPA) axis and the parallels which exist between the environmental stressors which provoke the onset of animal models of depression and those which provoke the onset of clinical depression

Animal model of depression	Type of stressor	HPA activation	Neurobiology of behavioural deficit	Reference
Immobility in forced swim test in rats	Entrapment	Yes	Model dependent on GR activation in hippocampus	de Kloet <i>et al.</i> 1988 ⁸⁸
Learned helplessness in rats	Entrapment	Yes	Model dependent on GR activation in hippocampus	Papolos <i>et al.</i> 1993 ⁹¹
Social subordination in rats in visible burrow system	Humiliation	Yes	Down-regulation of hippocampal 5HT _{1A} receptors in most 'depressed' rats	McKittrick <i>et al.</i> 1995 ⁹²
Loss of hierarchy in sugar sliders	Loss Humiliation	Yes	Not known	Mallick <i>et al.</i> 1994 ¹⁰⁵

Underlying mechanisms and implications for treatment

The first two sections of this review have described the changes that are seen in the HPA axis in animal models of chronic stress and in depressive illness: both are characterised by an up-regulation of the central drive to the HPA axis and a down-regulation of its negative feedback control. The third section described how many of the causes of depression themselves activate the HPA axis and the fourth section described how activation of the HPA axis can bring about both the onset of depression and possibly its continuation. This final section will consider the underlying mechanisms and their implications for treatment.

The simplest explanation for these observations is that the environmental influences which bring about the onset and continuation of depression themselves result in a central activation of the HPA axis followed by a secondary down-regulation of its negative feedback control. In theory it is possible that the primary site of action of these influences might be to down-regulate GRs since it is known that in transgenic animals with impaired GR function that a secondary activation of the HPA axis develops¹⁰⁶. This possibility cannot be

ignored, but because a central activation of the HPA axis is the first neuroendocrine component of the stress response and because depression is brought about by environmental stress, it is simplest to assume that a central activation of the HPA axis is the first change to develop in depressive illness and that down-regulation of GRs is a secondary effect. Genetic variation (polymorphism) of the GR may, however, explain the otherwise unexplained finding that only 50% of patients with endogenous or melancholic depression show hypercortisolaemia²³ and that only 50% of patients with Cushing's syndrome develop depression.

A number of findings described in this review point to the possibility, first raised by Deakin and Graeff⁵⁷, that the effects of social adversity on depression may be mediated by a down-regulation of hippocampal 5HT_{1A} receptors by corticosteroids. Both stress and corticosterone have been shown to down-regulate hippocampal 5HT_{1A} receptors in experimental animals¹⁰⁷⁻¹¹⁰, although discrepant findings have also been reported¹¹¹⁻¹¹⁵. In man, there is at present no measure of hippocampal 5HT_{1A} receptor function although there is evidence that cortisol can down-regulate 5HT_{1A} receptor mediated neuroendocrine^{116,117} and hypothermic responses¹¹⁸.

If hypercortisolaemia can bring about the onset of depression^{57,119} and perpetuate a depressive illness, then treatment strategies to counter this effect can be developed. This review has already indicated that because of the increased central drive to the HPA axis large doses of cortisol synthesis inhibitors are needed to normalise plasma cortisol in hypercortisolaemic depressives and for the same reason large doses of glucocorticoid receptor antagonists may be needed to obtain a therapeutic effect. An alternative strategy would be to target the negative feedback mechanisms. It so happens that many of the currently employed antidepressant drugs do up-regulate GRs and MRs in the hippocampus¹²⁰⁻¹²² and this effect may be a common action of all antidepressant treatments. It will be recalled that hippocampal GRs have been implicated in animal models of depression^{88,90,91} and so it is intriguing to note that antidepressant drugs can directly up-regulate these same receptors *in vitro*. Further studies are needed to determine whether in man antidepressant drugs up regulate GRs and MRs and whether this effect alters HPA axis function and hippocampal 5HT_{1A} receptors. Most important of all is the possibility that drugs developed specifically to up-regulate GRs and 5HT_{1A} receptors may prove to be a superior class of antidepressant drug.

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