Psychological Medicine (2013), **43**, 449–469. © Cambridge University Press 2012
doi:10.1017/S0033291712000955

REVIEW ARTICLE

Cortisol and depression: three questions for psychiatry

J. Herbert*

Cambridge Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK

Background. Cortisol plays a multifaceted role in major depression disorder (MDD). Diurnal rhythms are disturbed, there is increased resistance to the feedback action of glucocorticoids, excess cortisol may induce MDD, basal levels may be higher and the post-awakening cortisol surge accentuated in those at risk for MDD. Does this suggest new avenues for studying MDD or its clinical management?

Method. The relevant literature was reviewed.

Results. Cortisol contributes to genetic variants for the risk for MDD and the way that environmental events amplify risk. The corticoids' influence begins prenatally, but continues into adulthood. The impact of cortisol at each phase depends not only on its interaction with other factors, such as psychological traits and genetic variants, but also on events that have, or have not, occurred previously.

Conclusions. This review suggests that the time is now right for serious consideration of the role of cortisol in a clinical context. Estimates of cortisol levels and the shape of the diurnal rhythm might well guide the understanding of subtypes of MDD and yield additional indicators for optimal treatment. Patients with disturbed cortisol rhythms might benefit from restitution of those rhythms; they may be distinct from those with more generally elevated levels, who might benefit from cortisol blockade. Higher levels of cortisol are a risk for subsequent depression. Should manipulation of cortisol or its receptors be considered as a preventive measure for some of those at very high risk of future MDD, or to reduce other cortisol-related consequences such as long-term cognitive decline?

Received 31 October 2011; Revised 3 April 2012; Accepted 5 April 2012; First published online 8 May 2012

Key words: Brain, cortisol, depression, prevention, therapy.

Introduction

There is little doubt that cortisol plays a central role in the onset and course of major depression disorder (MDD) but considerable uncertainty over exactly what that role might be. Diurnal rhythms in cortisol are disturbed in around half the cases of major depression (Sachar *et al*. 1973); there is increased resistance to the feedback action of glucocorticoids on the activity of the hypothalamo–pituitary–adrenal (HPA) axis in a proportion of cases (Carroll *et al*. 1968; Carroll, 1982); the post-awakening surge in cortisol is accentuated in those at risk for MDD (Portella *et al*. 2005); prolonged excess corticoids, whether endogenous (as in Cushing's syndrome) or exogenous (therapeutic), may result in depression (Butler & Besser, 1968; Jeffcoate *et al*. 1979; Lewis & Smith, 1983); and morning cortisol levels at the higher end of the normal range are a risk factor for subsequent depression (Goodyer *et al*. 2000; Harris *et al*. 2000). Can we make sense of these disparate findings? Are these changes in cortisol epiphenomena of depression, or do they play a substantial role in the onset, recovery or course of a depressive episode? That is, are they cause or effect? Indeed, should assessment of cortisol play any part in routine clinical management of MDD? Could this be used either diagnostically or therapeutically?

The true meaning of the role of cortisol is only apparent in the context of a schema for the development of MDD. This schema is limited by uncertainties over the definition of MDD, which will remain as long as symptoms are the only means to define it, by doubts about the validity of the psychological concepts used to describe risk patterns, by a lack of physiological attributes of MDD, and by difficulties of combining measures from very different disciplines into a coherent account of the trajectories that lead to MDD. Any schema is therefore certainly incomplete and probably

* Address for correspondence: Professor J. Herbert, Cambridge Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK.
(Email: jh24@cam.ac.uk)

inaccurate. Nevertheless, we need to see how far we can fit cortisol into one. In this review, we address the following questions:

(1) Could information about cortisol levels and their daily variation guide improved understanding of subtypes of MDD and yield additional indicators for optimal treatment?
(2) Could restoration of disturbed cortisol rhythms and/or cortisol receptor blockade form part of the treatment of different forms of MDD?
(3) Could manipulation of cortisol in those at increased risk of MDD form part of a preventive strategy?

Several principles underlie the role of cortisol: (i) there are a number of predisposing factors (including cortisol) for subsequent MDD, and these interact; (ii) these factors may well exert their influence throughout the lifespan; (iii) the way each factor operates, and the influence that it has, will change at different stages of the lifespan; (iv) the effect(s) of each factor will depend not only on their contemporaneous interaction but also on events that have (or have not) occurred previously; and (v) the response of the brain to agents such as cortisol (but also to environmental events) will change with age. Thus there is a chain of probabilistic events that, in sequence, increase or decrease the likelihood of MDD. How are these influenced by cortisol?

Cortisol rhythms and MDD

Alterations in the diurnal rhythms of cortisol are well known to occur in some cases of MDD. About 50% of patients with MDD show elevated evening levels (Claustrat *et al*. 1984; O'Brien *et al*. 2004) related to increased pulsatile release of cortisol (Deuschle *et al*. 1997). Not all reports agree on this: exceptions include elevated morning cortisol or no change at all (Bridges & Jones, 1966; Koenigsberg *et al*. 2004). Efforts to relate variations in the clinical symptoms of MDD to cortisol rhythms have not been very successful (Veen *et al*. 2010; Vreeburg *et al*. 2010). Depressive symptoms even in very young children are also associated with increased HPA activity (Luby *et al*. 2003). Adrenal gland volumes may be increased (Rubin *et al*. 1995). It is not clear whether these reflect different types of depression or different samples. If we are to assess these changes, we need to consider the implications of altered cortisol rhythms.

Cortisol is secreted as a series of ultradian pulses (shorter than a day, but longer than an hour), and these vary in amplitude and frequency. Altered pulses underlie both diurnal rhythms in cortisol, which are very prominent, and the reaction to stressful events (Lightman & Conway-Campbell, 2010) (Fig. 1). Defining the precise nature of altered cortisol is not straightforward. For example, higher cortisol in the morning will increase the overall (mean) daily value, but also the amplitude of the diurnal rhythm (if levels later in the day do not alter). Either parameter may have specific consequences for brain function. Either pattern can be altered selectively in other ways; for example, both morning and evening levels can increase proportionately, thus increasing mean exposure but not altering the rhythm. Elevated morning levels may be the consequence of increased pulse amplitude, frequency, or both. Each ultradian pulse can result in a corresponding activation of a set of genes, although whether different frequencies of ultradian pulses result in different patterns of gene activation remains uncertain (Hazra *et al*. 2007; Conway-Campbell *et al*. 2010; McMaster *et al*. 2011). Finally, the brain's response may also depend on the duration of altered cortisol: whether hours, days or weeks.

Cortisol as a driver of the circadian system

Cortisol is not only part of the circadian system; it also helps to organize it. There is a more general disturbance in circadian physiology in MDD, including sleep and body temperature rhythms (von Zerssen *et al*. 1985; Wirz-Justice, 2006). Early awakening and altered temperature and melatonin cycles occur in MDD; in recovered patients, they resume a more normal pattern (Hasler *et al*. 2010). The hypothalamic suprachiasmatic nucleus (SCN) generates the circadian rhythm through interplay between the phasic expression of several genes, including *per1* and *per2*, *bmal1*, *cry* and *clock*, which are synchronized to the 24-h light–dark cycle by signals from the eyes (Hastings *et al*. 2008). Other tissues, including parts of the brain (e.g. the hippocampus), also express these 'clock' genes. Some, but not all, of these are synchronized by the daily corticoid rhythm (Maywood *et al*. 2006, 2007). For example, the phasic expression of *per2* in the hippocampus, but not the SCN, is driven by the daily rhythm of corticosterone in rats (Gilhooley *et al*. 2011). Other genes, not themselves part of a 'clock' mechanism, also respond phasically to corticoids. Thus, disturbances in the corticoid rhythm can have several consequences for gene expression in target organs (including the brain): altered rhythms in dependent clock genes; altered rhythms in genes driven by the daily corticoid rhythm; and desynchronization of those genes that are corticoid dependent from those that are not and that may continue their normal cyclicity (Hasler *et al*. 2010). Desynchronization and disruption of the normal circadian programme can have behavioural consequences similar to MDD, as in the

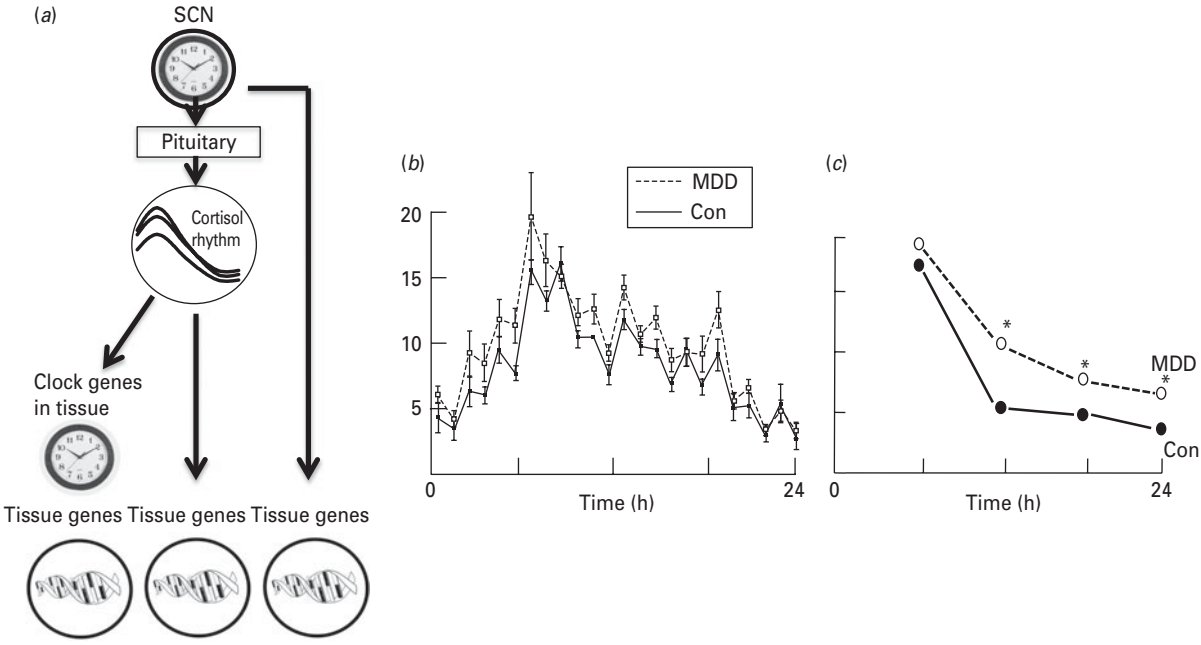

Fig. 1. (*a*) The entrainment of dependent genes by the circadian clock. The diurnal cortisol rhythm is generated by the 'clock' genes of the suprachiasmatic nucleus (SCN) acting through the pituitary (adrenocorticotrophic hormone, ACTH) and thence the adrenal cortex. (*Left*) Rhythmic cortisol secretion entrains '*clock*' genes in target tissues (including the brain) or (*centre*) acts directly on corticoid-responsive genes. Other peripheral rhythms (*right*) are entrained independently of cortisol. (*b*) Ultradian pulses of cortisol underlying the circadian cortisol rhythm in control (Con) and depressed (MDD) subjects (from Young *et al*. 2001). (*c*) The shape of the daily rhythm as it appears from four samples per day. Samples from older depressed subjects have blunted afternoon and evening nadirs compared to controls. * Indicates significant difference between controls (Con) and those with depression (MDD) (Drawn from data in O'Brien *et al*. 2004.)

phenomenon of jetlag, characterized by a lowered sense of well-being, depressed mood and impaired cognitive ability (Srinivasan *et al*. 2010; Menet & Rosbash, 2011).

Cortisol and awakening

For 30–60 min after awakening there is a surge of cortisol secretion (Hucklebridge *et al*. 1998). The awakening response is not itself a rhythmic event because it is linked to wakening, although sleep is part of diurnal rhythmic activity. The significance of the cortisol awakening response (CAR) has been much discussed, and remains unclear (Clow *et al*. 2004). This makes any association with MDD difficult to interpret. Moreover, the literature on CAR is not consistent. Poor parenting, a known risk factor for later MDD, is associated with increased CAR (Engert *et al*. 2011), but lower values were reported in those at high risk for MDD or with subclinical depressive symptoms (Dedovic *et al*. 2010). Others report increased CAR both in high-risk subjects and in those with MDD (Bhagwagar *et al*. 2005; Mannie *et al*. 2007), and also an association with a history of maternal MDD and low positive emotionality (Dougherty *et al*. 2009). Claims that the CAR may indicate vulnerability to MDD are limited until its significance is better understood, and its relationship to other genetic, psychological and social measures has been more firmly established.

Cortisol as a risk factor for MDD

Levels of morning cortisol in the higher range of normality are one risk factor for subsequent MDD (Goodyer *et al*. 2000; Harris *et al*. 2000) and higher cortisol is associated with MDD in cases of myocardial infarction (Otte *et al*. 2004) (Fig. 2). Altered cortisol rhythms may be another (Wichers *et al*. 2008). We know from other contexts that excess corticoids can endanger the brain, making it more vulnerable to noxious agents that, in the absence of raised corticoids, would not necessarily be damaging (Masters *et al*. 1989; Tombaugh *et al*. 1992). We can translate this notion to MDD: because we know that adversity (both early in life and more proximally) predisposes to MDD (Parker & Brown, 1982; Brown *et al*. 1987) (Kendler *et al*. 2004), higher cortisol may potentiate the psychopathological actions of these agents in a similar way (Gubba *et al*. 2000). The problem here is a pragmatic one: it has proved very difficult to

https://doi.org/10.1017/S0033291712000955 Published online by Cambridge University Press

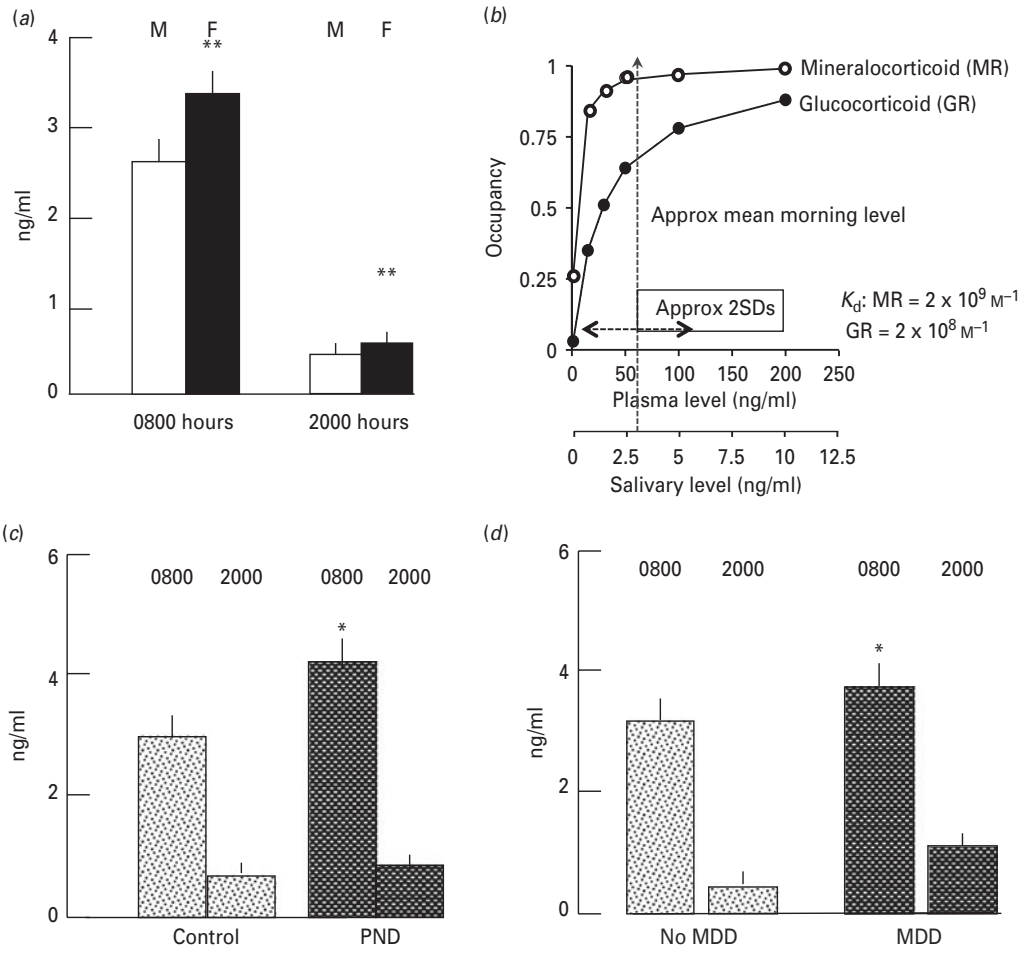

Fig. 2. (*a*) Gender differences in salivary cortisol in non-depressed male (M) and female (F) adolescents (after Netherton *et al*. 2004). (*b*) Saturation curves for glucocorticoid (GR) and mineralocorticoid receptors (MR), showing that MR is saturated at normal morning (but not evening) cortisol levels, whereas GR is not. This assumes that cerebrospinal fluid (CSF) and salivary levels of cortisol are similar (see text). (*c*) Higher morning cortisol at age 13 in offspring of mothers with postnatal depression (PND), and hence impaired maternal behaviour (from Halligan *et al*. 2004). (*d*) Higher morning levels of salivary cortisol in non-depressed adolescents who will develop first-onset major depression disorder (MDD) during a 4-year follow-up (from Goodyer *et al*. 2000). * Indicates a significance level of $p < 0.05$ between the two groups; ** $p < 0.01$.

measure cortisol in the days or weeks following individual life events, and thus predict from this measure whether the probability of subsequent MDD is altered.

Corticoids act on the mineralo- and glucocorticoid receptors (MRs and GRs) and hence downstream genes (Joels & de Kloet, 1994). GRs are widely distributed in the brain (including the frontal and cingulate cortices), but particularly highly concentrated in the hippocampus, amygdala and hypothalamus (Rosenfeld *et al*. 1993). MR expression is much more limited to these limbic areas (Reul *et al*. 2000), but has also been implicated in MDD (Young *et al*. 2003). Which area, or receptor type, might be involved in the risk represented by altered morning cortisol is not obvious (de Kloet *et al*. 2007), although because MRs are largely saturated by fairly modest levels of cortisol, excess levels are more likely to be sensed by GRs. (Fig. 2). Neither can we easily follow the trail offered by GR- or MR-responsive downstream genes as there are many that possess glucocorticoid response elements (GREs) (Santos *et al*. 2011). GREs have a variety of effects on other genes, including chromatin modifications (e.g. deacetylation) and recruitment of co-factors that may moderate glucocorticoid action (Santos *et al*. 2011). Another complication is that some genes that respond to corticoids, such as brain-derived neurotrophic growth factor (BDNF), do not contain a GRE. Action on them must therefore be indirect. Corticoids also act on membrane-bound receptors (e.g. *N*-methyl-D-aspartate, NMDA), which may have more direct, non-genomic, actions on neuronal function. Both glutamate and gamma-aminobutyric acid (GABA), which can respond to corticoids, have

https://doi.org/10.1017/S0033291712000955 Published online by Cambridge University Press

been implicated in MDD (Gutierrez-Mecinas *et al*. 2011).

The paragraphs above presuppose that we know what is meant by an 'optimal' level of cortisol but, in truth, this is far from clear (Herbert *et al*. 2006). 'Normal range' values may simply reflect individual variations in requirements for cortisol. Optimal levels vary even within an individual according to circumstance: Addisonian patients need different amounts of corticoids and are required to increase their dose if they become ill (Reisch & Arlt, 2009). We can suppose, therefore, that there are individual optimal ranges for cortisol, whether defined in absolute terms or as the shape or amplitude of the daily cortisol rhythm. These may vary both between and within individuals according to current circumstances. What determines this optimal range is currently unknown, but deviations from it may predispose the individual to the psychopathological effects discussed here.

Cortisol as a reflection of the interaction between genes and environment

What determines individual differences in cortisol levels? The limited studies on monozygotic (MZ) and dizygotic (DZ) twins suggest that genetic factors account for 50–60% of the variance (Hainer *et al*. 2001; Ouellet-Morin *et al*. 2008). The identities of the genes responsible are mostly unknown, although variants in the promoter region of the serotonin transporter (*hSERT*, *5HTTLPR*, *SLC6A4*) may contribute ('s' variants have higher levels) (Chen *et al*. 2009; Goodyer *et al*. 2009). The same gene is held to accentuate reactions to adverse life events (Caspi *et al*. 2003), which may, in turn, alter cortisol. Gender is another factor: both female rats and humans have higher levels of glucocorticoids (cortisol or corticosterone) than males (Netherton *et al*. 2004; Lightman *et al*. 2008) (Fig. 2). Oestrogens have a positive action on cortisol and corticosteroid-binding globulin (CBG) levels (Feldman *et al*. 1979; White *et al*. 2006), which may account for the fact that this sex difference is not observed in prepubertal children (Netherton *et al*. 2004). It is noteworthy that there is a marked excess of MDD in postpubertal females: do their increased cortisol levels contribute to this gender difference? Early adversity, for example impaired parenting resulting from maternal depression, may have lasting consequences for raised morning cortisol and the risk for MDD in later life (Halligan *et al*. 2004) (Fig. 2). The effect of early adversity on later cortisol levels might well be moderated by genetic variants in the child, such as the Val^{66}Met polymorphism in BDNF (Kaufman *et al*. 2006), although this has not yet been determined.

Early adversity can also accentuate the HPA response in later life to demand or 'stress' (Engert *et al*. 2010; van der Vegt *et al*. 2010; Hunter *et al*. 2011). Additional cortisol may itself represent an added risk for a psychopathological outcome; or cortisol may be simply a proxy for, or indicator of, accentuated stress responses, contributing nothing to the psychological outcome of those events. The evidence strongly points to the first proposition. As mentioned previously, Cushing's disease or prolonged corticosteroid therapy is known to induce MDD, but also mania (Starkman *et al*. 1981). Corticosterone accentuates the impact of fear-inducing stimuli in experimental animals (Roozendaal *et al*. 2009; Zamudio *et al*. 2009), and short-term administration to humans males has a similar effect (Merz *et al*. 2010) (although we should bear in mind the possible differences on behaviour of long- or short-term raised cortisol, discussed later).

Glucocorticoid feedback and depression

Increased resistance of the HPA axis to the feedback effect of dexamethasone (dexamethasone suppression test, DST) on blood cortisol levels in some cases of MDD was reported 40 years ago (Carroll, 1982, 1986). The high hopes that this might evolve into a laboratory test for MDD have not been realized. Neither has the DST given much insight into the derangement of the HPA axis in MDD. Various modifications, such as measuring the cortisol response to corticotrophin-releasing factor (CRF) following suppression by dexamethasone, have not improved the situation markedly, although there have been contrary claims (Holsboer *et al*. 1994). Dexamethasone is a 'pure' glucocorticoid (i.e. it has little action on MR) but there are several problems with the DST. It is not specific for MDD (even if the latter is a single disease); for example, food restriction induces a positive DST (Mullen *et al*. 1986), and only a proportion of MDD cases qualify as non-suppressors (the definition is an arbitrary one) (Brown & Shuey, 1980). There have also been claims that the DST differentiates different types of MDD (e.g. 'primary' and 'secondary' depression) (Schlesser *et al*. 1980) but this has not been established. Dexamethasone penetrates the blood–brain barrier rather poorly, and is exported by the P-glycoprotein transporter (Uchida *et al*. 2011). Thus the physiological information offered by the DST is unclear. The simple notion that it indicates a high drive state of the HPA axis is not convincing because correlations between the DST and basal levels of cortisol are not consistent (Asnis *et al*. 1982; Pfohl *et al*. 1985; Kathol *et al*. 1989; Rush *et al*. 1996).

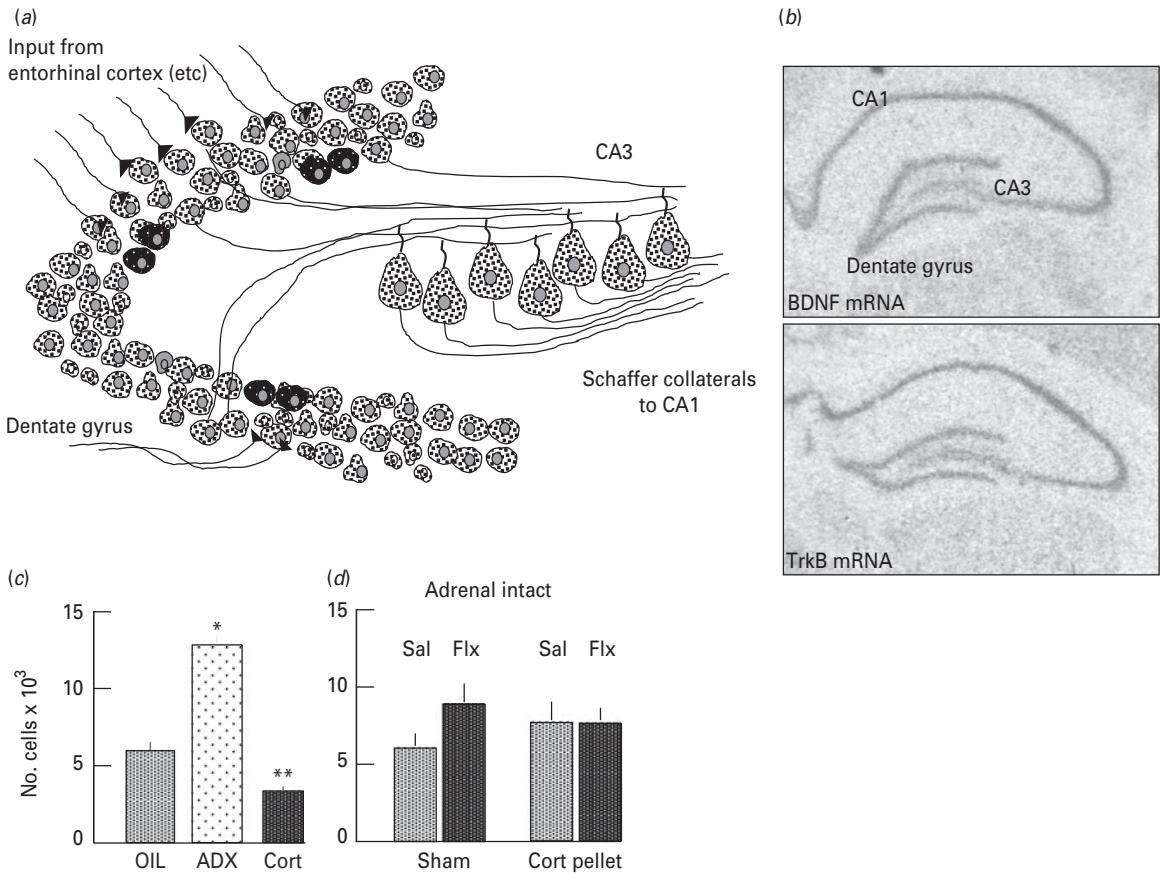

Fig. 3. (*a*) Neurogenesis in the adult hippocampus. The darker cells in the inner layer of the dentate gyrus are dividing progenitor cells. (*b*) *In situ* hybridizations showing high levels of brain-derived neurotrophic growth factor (BDNF) and tropomyosin-related kinase B (TrkB) receptor mRNAs in the hippocampus of the rat (from Pinnock *et al*. 2010). (*c*) Adrenalectomy (ADX) increases the number of dividing progenitor cells in the dentate gyrus whereas excess cortisocosterone (Cort) suppresses it. OIL injected animals are controls. (*d*) Fluoxetine (Flx) increases progenitor cell division (mitosis) in control rats, but not those in which the daily cortisoterone rhythm has been clamped by subcutaneous implant of a pellet of corticosterone (from Huang & Herbert, 2006). * Indicates a significance level of $p < 0.05$ between the two groups; ** $p < 0.01$.

Cortisol as a moderator of response to treatment

Elevated cortisol in MDD suggests that blocking GRs (e.g. with mifepristone) might be useful. Some report rapid resolution of symptoms (Belanoff *et al*. 2001; Flores *et al*. 2006), others less dramatic results (Simpson *et al*. 2005). There has been little attempt to relate response to this treatment with prevailing differences in cortisol secretion, or to consider whether a time-dependent use of drugs such as mifepristone might be required in some cases (for example, to restore the normal cortisol rhythm and sensitize patients to antidepressants). It should be noted that mifepristone also antagonizes progesterone receptors. Of note, a case of Cushing's-induced psychosis responded to mifepristone (Chu *et al*. 2001), supporting the notion that corticoid-dependent forms of MDD might respond to GR blockade. Clearly much more information on the contribution of GR antagonists to the treatment of MDD is required; a simple overall blockade might not be the optimal approach in some cases of established MDD (e.g. those with disordered rhythms). There are reports of improved mood in MDD subjects after either a cortisol infusion (Goodwin *et al*. 1992) or dexamethasone in a dose that would suppress elevated cortisol (Dinan *et al*. 1997). Can these results be reinterpreted in the light of the more complex ideas about variations in cortisol in MDD set out above? Behavioural approaches to treatment (e.g. cognitive behavioural therapy, CBT) might also be sensitive to either endogenous patterns of cortisol or imposed alterations in corticoid activity: this avenue should no longer be ignored.

Disordered corticoids may contribute to the ineffectiveness of antidepressant treatment. This is illustrated by the action of glucocorticoids on the hippocampus. The granule neurons of the dentate gyrus, the major input zone to the hippocampus from the

https://doi.org/10.1017/S0033291712000955 Published online by Cambridge University Press

entorhinal cortex and the site of adult neurogenesis, project to the large pyramidal cells of layer CA3 in the 'cortical' hippocampus; these, in turn, project, through the Shaffer collaterals, to the pyramidal cells of CA1 (Fig. 3). There is a complex non-uniform pattern of gene expression throughout CA1 (Dong *et al*. 2009). Different parts of the hippocampus may be involved in many neural disorders, including MDD (Small *et al*. 2011). Because the hippocampus expresses very high concentrations of both GRs and MRs (de Kloet *et al*. 2000), and is highly sensitive to glucocorticoids, it is essential to consider the consequences of altered cortisol on its structure and function and how they might relate to MDD.

The formation of new neurons (neurogenesis) in the hippocampus of adult rats is exceedingly sensitive to corticosterone. Giving rats excess corticosterone markedly reduces the mitosis rates of hippocampal progenitor cells and the survival of newly formed neurons (Wong & Herbert, 2004, 2006) (Fig. 3). Hippocampal neurogenesis also occurs in man (Eriksson *et al*. 1998), although it is not known whether it is moderated by cortisol. Serotonin-acting drugs, such as selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine) increase progenitor mitosis rates in rats, although only after about 14 days of continuous treatment, and may act on the GR (Malberg *et al*. 2000; Anacker *et al*. 2011). It is this fact, together with reports that some of the behavioural actions of SSRIs are prevented if increased neurogenesis is also blocked, that has encouraged the idea that altered hippocampal neurogenesis is in some way related to either the onset of depression or the therapeutic action of antidepressant drugs (Duman *et al*. 1999; Malberg, 2004). Flattening the daily corticosterone rhythm in rats prevents fluoxetine from stimulating progenitor mitosis, an effect that can be reconstituted by adding a daily injection of corticosterone, thus reinstating the daily rhythm (Huang & Herbert, 2006; Pinnock *et al*. 2007) (Fig. 3). A considerable proportion of depressed subjects do not respond to antidepressant drugs such as fluoxetine (around 40% in some reports) (Birkenhager *et al*. 2006). We do not know whether non-response is related to distorted daily cortisol rhythms, or whether restitution of these rhythms (for example by administration in the morning of a low dose of cortisol) might assist pharmacological responsiveness. Such investigations might be highly informative.

Neurogenesis is not the only way that excess glucocorticoids can alter the adult hippocampus. Repeated stress results in atrophy of the apical dendrites of CA1 neurons (Watanabe *et al*. 1992), a result replicated by excess corticosterone in both intact rats and tissue culture (Magarinos & McEwen, 1995; Alfarez *et al*. 2009). Both GR blockade and inhibition or knockdown of the NMDA receptor prevents this, by an action on CA3 and on CA1 (Christian *et al*. 2010). It seems clear that the whole of the three-neuron hippocampal circuit is extremely sensitive to corticoids. How this translates into an improved understanding of MDD is considered in the following sections.

Cortisol interactions with CRF

Any discussion of the HPA axis cannot ignore the role of corticotropin-releasing factor (CRF). Like other peptides, its name underestimates its function, which is to coordinate an adaptive response to stress that includes not only endocrine but also autonomic and behavioural responses (Mayer & Baldi, 1991; Herbert, 1993). CRF drives the HPA system (in association with other factors, including arginine vasopressin, AVP) and also responds to alter-ations in cortisol. This response may differ according to region: corticoids suppress hypothalamic CRF but increase levels in the amygdala (Schulkin, 2011). Because the amygdala is involved in fear and anxiety reactions, this is of particular interest. Experimentally, CRF increases anxiety (Britton *et al*. 1982). There are reports of elevated CRF levels in the cerebrospinal fluid (CSF) of depressed subjects (Arborelius *et al*. 1999). Although there are those who would ascribe depression itself to CRF (Binder & Nemeroff, 2010), it seems more likely that CRF is related either to co-morbid anxiety, a frequent occurrence in MDD, or to the disordered HPA axis described earlier.

Nevertheless, increased attention should be given to the possibility that altered CRF or its receptors, particularly in the amygdala, may interact with cortisol during episodes of MDD and other stress-related illnesses, or during the run-in to the onset of an episode following an adverse life event (Bao & Swaab, 2010), and play a role in either disordered cortisol secretion or the development of associated anxiety states. The clinical problem is that direct methods of measuring changes in CRF (unlike cortisol) are not available at present. Genetic variants in its receptor have been studied in the context of MDD without much success (Lewis *et al*. 2011) and, so far, attempts to develop new drugs for either depression or (more plausibly) anxiety disorders based on CRF have also not been very successful (Steckler, 2010).

Cortisol as a regulator of BDNF

There are numerous growth factors known in the brain, but it is BDNF that has been targeted as playing a special role in MDD. The evidence, still highly incomplete, comes from several sources. The basic

assumption is that either MDD is caused by maladaptive plasticity in the brain, or antidepressants act by allowing renewed plasticity that, in some way, restores normal function (Castren & Rantamaki, 2010). Exactly where this occurs, or how it might account for MDD, has not been specified, although the hippocampus is an obvious target: it has high concentrations of both BDNF and its principal receptor, tropomyosin-related kinase B (TrkB) (Fig. 3). BDNF is reduced in the brains of suicide victims, and drugs such as SSRIs increase levels in the hippocampus of both humans and rats (Chen *et al*. 2001; Karege *et al*. 2005). It is said that BDNF is crucial for the behavioural actions of antidepressants in experimental animals (Shirayama *et al*. 2002) but the current experimental 'models' of MDD lack convincing face and construct validity (discussed later). Nevertheless, only chronic treatments with SSRIs increase BDNF expression, consistent with the time-frame of the therapeutic response. Fluoxetine also increases plasticity in other parts of the central nervous system (CNS), such as the visual system (Maya Vetencourt *et al*. 2008), supporting the notion that this may be a mode of its action in MDD. BDNF is certainly crucial for the stimulating actions of fluoxetine on hippocampal neurogenesis and on the longer-term survival of new neurons (Sairanen *et al*. 2005; Pinnock *et al*. 2010).

Glucocorticoids have powerful effects on BDNF and on plasticity (Blugeot *et al*. 2011; Liston & Gan, 2011). Corticosterone reduces BDNF mRNA expression in the rat's hippocampus (Schaaf *et al*. 1998; Prickaerts *et al*. 2006). The stimulating action of SSRIs such as fluoxetine is prevented by excess corticosterone, probably because of inhibition of BDNF expression (Kunugi *et al*. 2010; Pinnock *et al*. 2010). Corticoids also repress the activity of TrkB (i.e. BDNF) receptors (Schaaf *et al*. 1997; Roskoden *et al*. 2004; Stranahan *et al*. 2011), thus accentuating and complicating their control of BDNF function.

There is a common polymorphism in the human *BDNF* gene (Val^{66}Met): about 30% of humans carry at least one copy of the Met allele. This alters the rate of secretion of pro-BDNF and BDNF. Because the two peptides act largely on different receptors (p75 and TrkB respectively), this would be expected to influence the way *BDNF* regulates neural function. Met carriers have smaller hippocampi and poorer episodic memory (Egan *et al*. 2003). Attempts to relate this polymorphism to risk for MDD have been inconsistent (Verhagen *et al*. 2010). It is now realized that defining the contribution of single gene polymorphisms to complex diseases is more informative if their interactions with specified environmental events (and other genes) are taken into account. The risk of later MDD following early adversity is greatest in those carrying the Met variant of the *BDNF* Val^{66}Met polymorphisms, but also in association with the 's' allele of *hSERT* (*5HTTLPR*) (Kaufman *et al*. 2006; Yang *et al*. 2009), although this was not confirmed in adolescents (Nederhof *et al*. 2010). They also have smaller hippocampi, prefrontal cortices and amygdalae, and more depressive symptoms (Gatt *et al*. 2009). The Met allele is also associated with MDD following an adverse life event (Bukh *et al*. 2009). By contrast, the power of morning cortisol to predict later MDD was accentuated in those carrying the Val variant (Goodyer *et al*. 2010). To reconcile these reports, which are not necessarily contradictory, we need information from a single, large sample on the way that this *BDNF* variant interacts with early adversity, proximal life events and the diurnal cortisol pattern, and with other common variants (such as *hSERT*) that are known to influence cortisol levels. Even though the literature is incomplete, the experimental and clinical evidence points to a powerful role for BDNF in MDD, and one that may be strongly influenced by cortisol, although this is still a subject for debate (Groves, 2007).

Cortisol as a moderator of the depressogenic actions of the immune system

Glucocorticoids are major controllers of the immune system (Flammer & Rogatsky, 2011) (Fig. 4). Despite long-standing indicators that the immune system is implicated in MDD, this area remains underresearched. One reason for this is uncertainty about whether peripheral measures of, say, cytokines tell us very much about what might be happening in the CNS. Even if CSF levels could be measured easily, this might not reflect local changes in regions of the brain.

The induction of MDD-like states following treatment with cytokines, such as interferon-α, offered the first clue (Piser, 2010). Stress increases neural cytokines, including interleukin (IL)-1β and IL-6 (Gadek-Michalska *et al*. 2008; Garcia-Bueno *et al*. 2008). Experimental intracerebral infusions of cytokines such as IL-1β or IL-6 induce a syndrome called 'sickness behaviour' (Lenczowski *et al*. 1999; Dantzer *et al*. 2008), which includes social withdrawal, cognitive impairment, anhedonia and increased activity of the HPA axis, a much more convincing 'model' for MDD than other more commonly used procedures such as rats struggling in warm water or mice suspended by the tail, the usual experimental methods of assessing 'depressive' behaviour (Dantzer, 2009) (Fig. 4). IL-1β also reduces neurogenesis (Gemma *et al*. 2007; Zunszain *et al*. 2012). There are persistent reports of elevated cytokines such as tumour necrosis factor (TNF)-α and IL-6 in the blood, and also C-reactive

https://doi.org/10.1017/S0033291712000955 Published online by Cambridge University Press

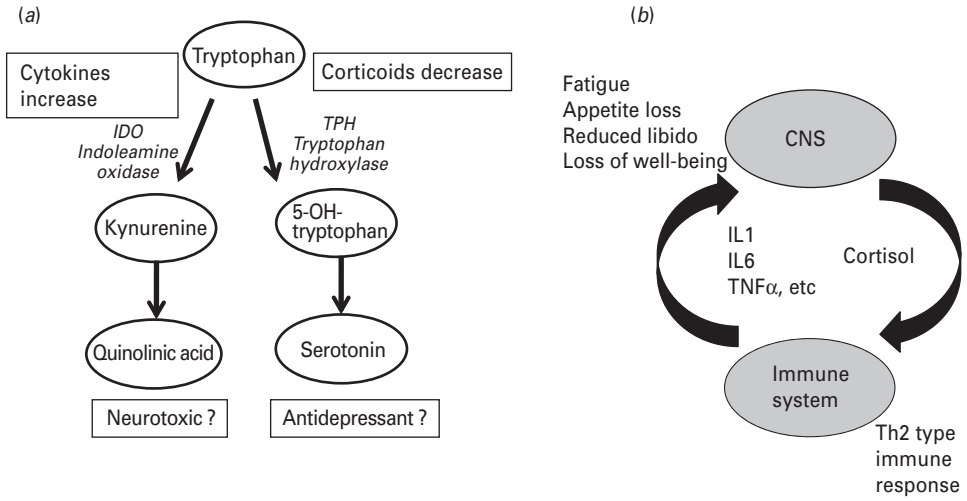

Fig. 4. (*a*) The two metabolic pathways of tryptophan (kynurenine and hence quinolinic acid, or 5-OH tryptophan and hence serotonin). (*b*) The reciprocal interactions between cortisol and the immune system. CNS, Central nervous system; IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumour necrosis-α; Th2, T-helper 2.

protein, in MDD (Kahl *et al*. 2006; Dowlati *et al*. 2010; Copeland *et al*. 2012), although we need to know how these are reflected in brain levels or function.

Glucocorticoids decrease the expression of tryptophan hydroxylase type 2 (TPH2), the brain isoform of this enzyme (Clark *et al*. 2008) (Fig. 4). This will both reduce serotonin and increase the activity of the alternative tryptophan pathway products (including the production of quinolinic acid, a neurotoxin), through indoleamine 2,3-dioxygenase (Capuron & Dantzer, 2003). This enzyme is stimulated by cytokines (Maes, 2011) and thus encourages the formation of quinolinic acid. Both processes may therefore contribute in parallel to MDD (Oxenkrug, 2010; Dantzer *et al*. 2011; Maes *et al*. 2011); antidepressants increase TPH2 (Heydendael & Jacobson, 2009).

There is a paradox: if corticoids reduce pro-inflammatory cytokines then higher levels should protect against MDD. However, pro-inflammatory cytokines may also interfere with GR activity, which suggests a more complex interaction (Pace & Miller, 2009). Furthermore, the interaction between cortisol and cytokines is two-way: cytokines stimulate HPA activity but cortisol may dampen the pro-inflammatory actions of cytokines. It may be that the balance between these interactions varies, so that in some cases one or other predominates (van der Meer *et al*. 1996).

Cortisol moderation by dehydroepiandrosterone (DHEA)

DHEA and its sulfate (DHEAS) are the most abundant steroids in the blood. Levels rise rapidly at adrenarche (around 8 years) to peak at about 20 years, and then decline progressively with age at individually variable rates (Orentreich *et al*. 1984, 1992). DHEA moderates the potency of cortisol on corticoid-sensitive tissues such as the thymus (May *et al*. 1990) and lymphocytes (Blauer *et al*. 1991; Buford & Willoughby, 2008); it prevents the suppressive actions of corticosterone on neurogenesis in the adult hippocampus (Karishma & Herbert, 2002); and levels have been reported to be lowered during MDD (Goodyer *et al*. 2000; Michael *et al*. 2000) and in other serious illnesses (Beishuizen *et al*. 2002). If the cortisol/DHEA ratio increases, then a given level of cortisol will gain potency. DHEA enters the CSF in about the same proportion as cortisol, but DHEAS much less, so that the proportion of the two forms in the CSF are not the same as in the blood (Guazzo *et al*. 1996).

The contribution of cortisol to the risk of MDD, its symptoms or progression may not be assessed accurately if current levels of DHEA are not taken into account. Because DHEA has such powerful actions on the immune system (Khorram *et al*. 1997; Buford & Willoughby, 2008), whether it moderates cytokine production in the brain, and hence MDD, needs to be assessed. DHEAS was unable to prevent 'sickness behaviour' induced by lipopolysaccharide (LPS) (Chen & Johnson, 2004), but there is no other information. We know nothing about the possible role of DHEA in stress reactions during the prenatal period. Cortisol/DHEA ratios are increased in treatment-resistant MDD (Markopoulou *et al*. 2009). DHEA has been tried as an antidepressant therapy with some success (Wolkowitz *et al*. 1999; Schmidt *et al*. 2005; Rabkin *et al*. 2006), but has not yet been accepted in clinical practice. There is an arguable case that DHEA therapy

https://doi.org/10.1017/S0033291712000955 Published online by Cambridge University Press

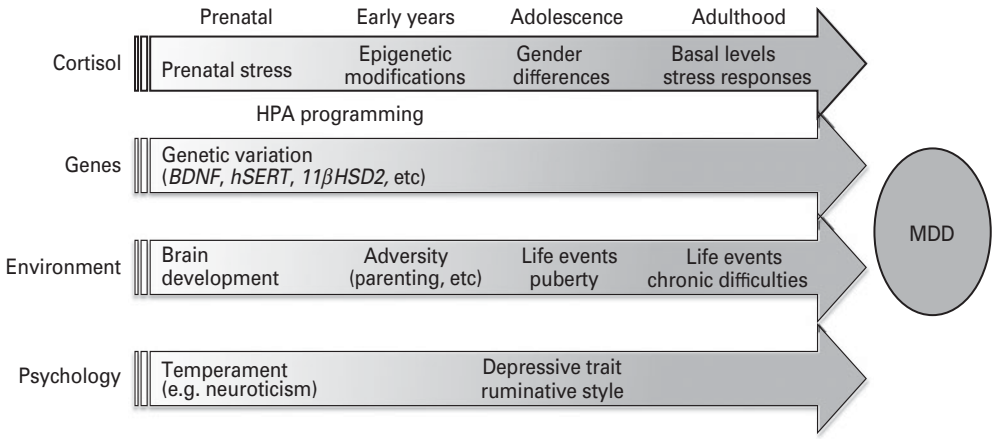

Fig. 5. Diagrammatic representation of the role of cortisol in the lifespan trajectories that predispose to the onset of major depression disorder (MDD). Each arrow represents the lifelong (but variable) influence of four major factors determining the risk for MDD. There are mutliple interactions (often bidirectional) between these four factors that vary according to stage of maturation and upon the presence or absence of preceding interactions. These are not shown in the figure but may be inferred, and are discussed in the text. HPA, Hypothalamo–pituitary–adrenal.

might be included together with the manipulations of cortisol described elsewhere in this review in future antidepressive therapies or preventive strategies. Cortisol tends to increase with age as DHEA declines (Lupien *et al*. 2009), so therapy incorporating DHEA may be particularly relevant in older people. DHEA protects hippocampal neurons against the neurotoxic effects of glutamate (Kimonides *et al*. 1998), so DHEA treatment might well diminish the risk of age-related neurodegeneration as well (Kohler *et al*. 2010; Franz *et al*. 2011).

Cortisol and the brain

Can we map these various actions of cortisol onto the brain? Because the symptoms of MDD include both emotional and cognitive components, this implicates potentially a considerable part of the brain. Nevertheless, the current evidence points to several brain regions that seem particularly involved in MDD, including various parts of the frontal lobe (orbital, area 25, anterior cingulate), the amygdala, the hippocampus and, perhaps, the habenula, which have established neural connections with each other (Almeida *et al*. 2003; Pezawas *et al*. 2005; Sartorius & Henn, 2007; Kennedy *et al*. 2011). It seems likely that MDD, even if it is a single disorder (a dubious assumption), represents a disorder of this network, and manipulations (e.g. electrical stimulation) of part of it may restore more normal function in the whole (Mayberg *et al*. 2005). Can we envisage cortisol acting as a similar nodal factor in part of this network? There are two caveats: the role of cortisol as a risk factor for MDD seems distinct from alterations that are part of the phenomenon of established MDD, as we have seen; and the widespread distribution of GRs within all the areas listed above, in addition to other equally widespread cellular actions such as those on glutamate, discourages such a conclusion. However, it remains plausible that the risk-enhancing actions of cortisol may be dependent upon effects either on a different cellular pathway or on a different part of the network from those during an episode of MDD. Furthermore, individual changes in regional differences in the sensitivity of the brain to corticoids set up, for example, by differential local epigenetic events may play a role in the way that cortisol influences particular cognitive or emotional functions.

Cortisol as a component of a schema for depression

How can the information on cortisol be integrated into an improved understanding of the processes leading to MDD? (Fig. 5). A simple schema for events immediately proximal to an episode of MDD would be: a severe life event occurs; and the response to this is moderated by the subject's temperament (reactivity), current levels of depressive symptoms (including self-esteem) and the cognitive response to the life event, such a ruminative thinking style (McLaughlin & Nolen-Hoeksema, 2011). These, of course, are not necessarily independent but depend upon antecedent factors. The precipitating event (such as a severe loss) triggers either a progressive process or an iterative one (e.g. ruminative thinking) that is represented by the latent period preceding the onset of MDD (several weeks or months). What these might be or where in the brain they happen is still obscure. Does cortisol play a role in these proximal or more distal events?

The process begins prenatally (Fig. 5). Genetic factors play a major part in determining risks for MDD. However, even in the protected environment of the uterus, prenatal events can influence later HPA function in ways that can influence the likelihood of subsequent MDD. The offspring of stressed pregnant rats show heightened corticosterone levels and increased levels of anxiety, fear and HPA responses to stress (Nishi *et al*. 2011). This can be replicated by treating dams with corticosterone, and prevented by removal of their adrenals, thus implicating exposure to increased prenatal corticoids (Salomon *et al*. 2011). Similar results follow reduction of 11beta-hydroxysteroid dehydrogenase type 2 (11βHSD2), which acts as a foetal barrier to maternal corticosterone (Seckl & Holmes, 2007). Prenatal dexamethasone treatment increases both basal and stress-induced cortisol levels in infant monkeys, and decreases the size of the hippocampus (Uno *et al*. 1994). Prenatal corticoids therefore contribute to postnatal behavioural traits (e.g. anxiety) and to HPA activity ('programming') in rats, although, as expected, they can be moderated by genetic variations such as those in the serotonin transporter (Belay *et al*. 2011). Other components of the HPA axis, including variations in CRF or its receptors, may also play a significant part in shaping the pre- and postnatal brain (Ivy *et al*. 2010). Do comparable events occur in humans? There are parallels (O'Regan *et al*. 2001) but the evidence is less complete. Although prenatal maternal stress can influence the child's later emotional and cognitive behaviour, whether corticoids are implicated remains unproven (Glover *et al*. 2010), although the weight of evidence from other species, including primates, makes it likely.

Alterations in corticoid receptor function are as important as those in the agonist (van Rossum & van den Akker, 2011). It is noteworthy that exonic polymorphisms (single nucleotide polymorphisms, SNPs) in *GR* and *MR* and also in the *11βHSD* genes are rare, suggesting that they are tightly conserved, unlike, for example, other genes associated with MDD such as *hSERT* or *BDNF*. It may be that any change in *GR* is deleterious (van Rossum *et al*. 2005), whereas a given variation in *hSERT* and *BDNF* may be either disadvantageous or even advantageous according to context (Homberg & Lesch, 2011). Variations in other genes that modulate *GR* function, such as *FKBP5*, or downstream variations in, for example, transcription factors, may contribute to individual risk (Zimmermann *et al*. 2011). We should also note that the contribution of MR and aldosterone, its principal agonist, to MDD have hardly been studied despite experimental evidence for the importance of MR/GR interactions (Joels & de Kloet, 1994; de Kloet *et al*. 2000) and evidence that MR variants may contribute to human emotionality (DeRijk *et al*. 2011).

Poor parenting may alter glucocorticoid-related genes (e.g. *GR*) in rodents by epigenetic modifications such as methylation (Alikhani-Koopaei *et al*. 2004; Meaney & Szyf, 2005; Szyf *et al*. 2005; McGowan *et al*. 2011). Methylation (or acetylation) of DNA alters a gene's expression for prolonged, even lifetime, periods (Fig. 5). Comparisons between rodents and humans must be tempered by the knowledge that rodents are born highly immature (altricial) compared to humans. Hence some of the postnatal processes described in rodents may occur prenatally in man. There was no alteration in *GR* methylation in the brains of suicide victims (Alt *et al*. 2010); however, methylation of *GR* in the blood was increased in infants with depressed mothers (Oberlander *et al*. 2008). Measuring methylation patterns in blood may not give an accurate representation of those in the CNS (Turner *et al*. 2010; Cao-Lei *et al*. 2011; Wiench *et al*. 2011). This area of research is only at its beginning.

The surge of MDD that occurs during adolescence and in subsequent years thus occurs on the back of pre- and postnatal events (Fig. 5), both influenced by cortisol. The contribution of gonadal steroids to the marked sex difference in the incidence of adolescent MDD needs further study. Oestrogens markedly increase total cortisol levels in the blood, but also those of CBG (Qureshi *et al*. 2007). There is a range of psychological variables that represent risks for MDD. They include: neuroticism, a component of 'personality' or 'temperament'; levels of subclinical depressive symptoms, which includes self-esteem, an appraisal of self-worth or value; and rumination, a cognitive style for dealing with adversity (Goodyer *et al*. 2003; Nolen-Hoeksema *et al*. 2011). Some are 'traits' and have thus been largely established by a variety of genetic and environmental interactions, many of them modulated by cortisol. The occurrence of an adverse life event is held to trigger an episode of MDD in many cases (Brown, 1986; Brown *et al*. 2010). As we have seen, an essential piece missing from the overall puzzle is whether this activates the HPA axis in particular ways that may contribute to the risk of MDD. Because basal (pre-morbid) levels of cortisol are a risk factor, we can conclude that any early agent setting these levels (e.g. poor parenting) will act as a distally derived but proximally active adjuvant for MDD. Thus cortisol, in whatever configuration (absolute levels, diurnal variation, etc.), plays a substantial (but variable) role at all points of the lifetime trajectory that may predispose to MDD. This also applies to the interaction between cortisol and common genetic variants such as those in the serotonin transporter and *BDNF*.

Is cortisol associated with individual differences in psychological measures? Some report no association between cortisol and temperamental characteristics such as 'emotionality' (neuroticism) (Schommer *et al*. 1999; van Santen *et al*. 2011). Others find positive associations between neuroticism and current cortisol levels (Nater *et al*. 2010) but these can be in either direction and are not consistent (Gerritsen *et al*. 2009). There are positive results for other characteristics, such as internalizing behaviour (Tyrka *et al*. 2010). Does cortisol affect current mood? Giving an acute dose of cortisol had no effect on mood (Wachtel & de Wit, 2001; Het & Wolf, 2007) but increased negative mood and response to unpleasant pictures, although only after repeated showings (Wirth *et al*. 2011). Cortisol may thus exert its actions on emotions in a situation-dependent manner. However, other studies show that cortisol did not reduce subjective fear responses in a socially demanding situation in normal subjects, but did reduce phobic fear (Soravia *et al*. 2006, 2009). Increased sensitivity to arousal occurred after neutral (not aversive) stimuli (Abercrombie *et al*. 2005), but negative mood following the Trier stress test was in fact reduced in healthy volunteers; those prone to develop MDD reacted differently (Het & Wolf, 2007).

The actions of cortisol on the brain may be very rapid (Strelzyk *et al*. 2012). Many studies have focused on memory, rather than mood. Cortisol decreased verbal (but not non-verbal) memory, without effects on executive function (Newcomer *et al*. 1999; Wolf *et al*. 2001). In subjects with MDD, dexamethasone in fact improved declarative memory (but not in controls) (Bremner *et al*. 2004). There is disagreement about whether cortisol enhances memory for emotionally arousing stimuli or for any stimulus irrespective of emotional valence (Buchanan & Lovallo, 2001; Abercrombie *et al*. 2003). Although there is some literature on the relationship between cortisol responses and ruminative style (Young & Nolen-Hoeksema, 2001; Zoccola *et al*. 2010), there is no information on whether induced elevations in cortisol can influence that style.

These short-term studies have limited value in the context of MDD because the period of exposure to increased levels is likely to be much more prolonged in the latter. Cushing's disease offers one opportunity to study the results of protracted excess cortisol on psychological processes such as self-esteem or ruminative style. However, nearly all studies compare Cushing's patients with controls, and there is no doubt that the former show affective disturbances (depression) and cognitive deficits (such as impaired emotional recognition) (Langenecker *et al*. 2012). Re-examining recovered Cushing's patients in the expectation that they return to a basal, pre-morbid state is vitiated by knowledge that recovery is often incomplete and the effects of hypercortisolaemia are prolonged (Pereira *et al*. 2010; Tiemensma *et al*. 2010). Prednisone therapy is associated with both depressive and antidepressive actions (Brown *et al*. 2010; Sun *et al*. 2011) in addition to impaired cognitive abilities (Brown, 2009), but pharmacological differences from cortisol and the presence of an underlying disease render conclusions relevant to MDD difficult.

Three questions about cortisol for psychiatry

What does current knowledge about the role of cortisol in MDD suggest for clinical investigation or application? We need to take into account the multiple interactions between cortisol and other risk factors for MDD, and the way these change as one phenomenon of the disorder itself. Cortisol exerts its influence across two dimensions: a time-related one based on phases of the lifespan that regulate levels of risk, and a more proximal one during the processes leading to the onset and course of an episode of MDD (Fig. 5). Cortisol plays a central role in the genetic contribution to MDD, as one expression of genetic variation, and on the way that environmental events predispose to MDD, as a response to that environment; that is, it plays a pervasive part in both sides of the G × E interaction. It is evident, both from this review and the literature at large, that consideration of the role of cortisol in isolation from other factors known to be concerned with either the risk of MDD or its course is not profitable. We can, however, address the three questions posed at the start of this review:

(1) Careful assessment of cortisol, genes and the symptoms in MDD will help us differentiate distinct categories of this complex disorder, and thus stratify subjects for selective treatment regimes. We should anticipate adequate cortisol measures (saliva, several time points, several days) as part of the routine management of MDD.
(2) Patients with disturbed cortisol rhythms might benefit from restitution of those rhythms; they may be distinct from those with more generally elevated levels, who might benefit from cortisol blockade. Selective manipulations of cortisol, based on adequate assessment of individual cortisol rhythms, should play a role in treatment (in combination with antidepressants or behavioural therapy). DHEA treatment might well play an adjunctive role, particularly in older patients with MDD.
(3) A careful assessment of the contribution of various risk factors for MDD might indicate the effect size of excess cortisol in individual cases as the risk for subsequent MDD. Manipulation of cortisol, its

https://doi.org/10.1017/S0033291712000955 Published online by Cambridge University Press

receptors or related molecules (to reduce the action of cortisol on the brain) should be considered as a preventive measure for some of those at very high risk of future MDD in which cortisol plays a significant role, in addition to preventing other cortisol-related consequences such as long-term cognitive decline.

Acknowledgements

I am deeply grateful to J. Bancroft, P. Cowen, I. Goodyer, A. Grossman, B. Keverne, S. Lightman and J. Schulkin, and also three anonymous referees, who made many valuable suggestions, nearly all of which I have adopted. I thank the Cambridge Centre for Brain Repair and its chairman, James Fawcett, for its hospitality. My work has been supported principally by grants from the Wellcome Trust and the UK Medical Research Council.

Declaration of Interest

None.

References

Abercrombie HC, Kalin NH, Davidson RJ (2005). Acute cortisol elevations cause heightened arousal ratings of objectively nonarousing stimuli. *Emotion* **5**, 354–359.

Abercrombie HC, Kalin NH, Thurow ME, Rosenkranz MA, Davidson RJ (2003). Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behavioral Neuroscience* **117**, 505–516.

Alfarez DN, De Simoni A, Velzing EH, Bracey E, Joels M, Edwards FA, Krugers HJ (2009). Corticosterone reduces dendritic complexity in developing hippocampal CA1 neurons. *Hippocampus* **19**, 828–836.

Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM (2004). Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. *Journal of Clinical Investigation* **114**, 1146–1157.

Almeida OP, Burton EJ, Ferrier N, McKeith IG, O'Brien JT (2003). Depression with late onset is associated with right frontal lobe atrophy. *Psychological Medicine* **33**, 675–681.

Alt SR, Turner JD, Klok MD, Meijer OC, Lakke EA, Derijk RH, Muller CP (2010). Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. *Psychoneuroendocrinology* **35**, 544–556.

Anacker C, Zunszain PA, Cattaneo A, Carvalho LA, Garabedian MJ, Thuret S, Price J, Pariante CM (2011). Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. *Molecular Psychiatry* **16**, 738–750.

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *Journal of Endocrinology* **160**, 1–12.

Asnis GM, Halbreich U, Nathan RS, Ostrow L, Novacenko H, Endicott J, Sachar EJ (1982). The dexamethasone suppression test in depressive illness: clinical correlates. *Psychoneuroendocrinology* **7**, 295–301.

Bao AM, Swaab DF (2010). Corticotropin-releasing hormone and arginine vasopressin in depression focus on the human postmortem hypothalamus. *Vitamins and Hormones* **82**, 339–365.

Beishuizen A, Thijs LG, Vermes I (2002). Decreased levels of dehydroepiandrosterone sulphate in severe critical illness: a sign of exhausted adrenal reserve? *Critical Care* **6**, 434–438.

Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF (2001). Rapid reversal of psychotic depression using mifepristone. *Journal of Clinical Psychopharmacology* **21**, 516–521.

Belay H, Burton CL, Lovic V, Meaney MJ, Sokolowski M, Fleming AS (2011). Early adversity and serotonin transporter genotype interact with hippocampal glucocorticoid receptor mRNA expression, corticosterone, and behavior in adult male rats. *Behavioral Neuroscience* **125**, 150–160.

Bhagwagar Z, Hafizi S, Cowen PJ (2005). Increased salivary cortisol after waking in depression. *Psychopharmacology* (*Berlin*) **182**, 54–57.

Binder EB, Nemeroff CB (2010). The CRF system, stress, depression and anxiety – insights from human genetic studies. *Molecular Psychiatry* **15**, 574–588.

Birkenhager TK, van den Broek WW, Moleman P, Bruijn JA (2006). Outcome of a 4-step treatment algorithm for depressed inpatients. *Journal of Clinical Psychiatry* **67**, 1266–1271.

Blauer KL, Poth M, Rogers WM, Bernton EW (1991). Dehydroepiandrosterone antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. *Endocrinology* **129**, 3174–3179.

Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, Bernard C, Benoliel JJ, Becker C (2011). Vulnerability to depression: from brain neuroplasticity to identification of biomarkers. *Journal of Neuroscience* **31**, 12889–12899.

Bremner JD, Vythilingam M, Vermetten E, Anderson G, Newcomer JW, Charney DS (2004). Effects of glucocorticoids on declarative memory function in major depression. *Biological Psychiatry* **55**, 811–815.

Bridges PK, Jones MT (1966). The diurnal rhythm of plasma cortisol concentration in depression. *British Journal of Psychiatry* **112**, 1257–1261.

Britton DR, Koob GF, Rivier J, Vale W (1982). Intraventricular corticotropin-releasing factor enhances behavioral effects of novelty. *Life Sciences* **31**, 363–367.

Brown ES (2009). Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. *Annals of the New York Academy of Sciences* **1179**, 41–55.

Brown ES, Denniston D, Gabrielson B, Khan DA, Khanani S, Desai S (2010). Randomized, double-blind, placebo-controlled trial of acetaminophen for preventing

mood and memory effects of prednisone bursts. *Allergy and Asthma Proceedings* **31**, 331–336.

Brown G (1986). Expressed emotion and life events in schizophrenia and depression. *Journal of Psychosocial Nursing and Mental Health Services* **24**, 31–34.

Brown GW, Bifulco A, Harris TO (1987). Life events, vulnerability and onset of depression: some refinements. *British Journal of Psychiatry* **150**, 30–42.

Brown WA, Shuey I (1980). Response to dexamethasone and subtype of depression. *Archives of General Psychiatry* **37**, 747–751.

Buchanan TW, Lovallo WR (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* **26**, 307–317.

Buford TW, Willoughby DS (2008). Impact of DHEA(S) and cortisol on immune function in aging: a brief review. *Applied Physiology, Nutrition, and Metabolism* **33**, 429–433.

Bukh JD, Bock C, Vinberg M, Werge T, Gether U, Vedel Kessing L (2009). Interaction between genetic polymorphisms and stressful life events in first episode depression. *Journal of Affective Disorders* **119**, 107–115.

Butler PW, Besser GM (1968). Pituitary-adrenal function in depression. *Lancet* **2**, 51.

Cao-Lei L, Leija SC, Kumsta R, Wust S, Meyer J, Turner JD, Muller CP (2011). Transcriptional control of the human glucocorticoid receptor: identification and analysis of alternative promoter regions. *Human Genetics* **129**, 533–543.

Capuron L, Dantzer R (2003). Cytokines and depression: the need for a new paradigm. *Brain, Behavior, and Immunology* **17** (Suppl. 1), S119–S124.

Carroll BJ (1982). Use of the dexamethasone suppression test in depression. *Journal of Clinical Psychiatry* **43**, 44–50.

Carroll BJ (1986). Informed use of the dexamethasone suppression test. *Journal of Clinical Psychiatry* **47**, 10–12.

Carroll BJ, Martin FI, Davies B (1968). Resistance to suppression by dexamethasone of plasma 11-O.H.C.S. levels in severe depressive illness. *British Medical Journal* **3**, 285–287.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**, 386–389.

Castren E, Rantamaki T (2010). Role of brain-derived neurotrophic factor in the aetiology of depression: implications for pharmacological treatment. *CNS Drugs* **24**, 1–7.

Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001). Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biological Psychiatry* **50**, 260–265.

Chen J, Johnson RW (2004). Dehydroepiandrosterone-sulfate did not mitigate sickness behavior in mice. *Physiology and Behavior* **82**, 713–719.

Chen MC, Joormann J, Hallmayer J, Gotlib IH (2009). Serotonin transporter polymorphism predicts waking cortisol in young girls. *Psychoneuroendocrinology* **34**, 681–686.

Christian KM, Miracle AD, Wellman CL, Nakazawa K (2010). Chronic stress-induced hippocampal dendritic retraction requires CA3 NMDA receptors. *Neuroscience* **174**, 26–36.

Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D (2001). Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *Journal of Clinical Endocrinology and Metabolism* **86**, 3568–7353.

Clark JA, Flick RB, Pai LY, Szalayova I, Key S, Conley RK, Deutch AY, Hutson PH, Mezey E (2008). Glucocorticoid modulation of tryptophan hydroxylase-2 protein in raphe nuclei and 5-hydroxytryptophan concentrations in frontal cortex of C57/Bl6 mice. *Molecular Psychiatry* **13**, 498–506.

Claustrat B, Chazot G, Brun J, Jordan D, Sassolas G (1984). A chronobiological study of melatonin and cortisol secretion in depressed subjects: plasma melatonin, a biochemical marker in major depression. *Biological Psychiatry* **19**, 1215–1228.

Clow A, Thorn L, Evans P, Hucklebridge F (2004). The awakening cortisol response: methodological issues and significance. *Stress* **7**, 29–37.

Conway-Campbell BL, Sarabdjitsingh RA, McKenna MA, Pooley JR, Kershaw YM, Meijer OC, De Kloet ER, Lightman SL (2010). Glucocorticoid ultradian rhythmicity directs cyclical gene pulsing of the clock gene period 1 in rat hippocampus. *Journal of Neuroendocrinology* **22**, 1093–1100.

Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ (2012). Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. *Biological Psychiatry* **71**, 15–21.

Dantzer R (2009). Cytokine, sickness behavior, and depression. *Immunology and Allergy Clinics of North America* **29**, 247–264.

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience* **9**, 46–56.

Dantzer R, O'Connor JC, Lawson MA, Kelley KW (2011). Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology* **36**, 426–436.

Dedovic K, Engert V, Duchesne A, Lue SD, Andrews J, Efanov SI, Beaudry T, Pruessner JC (2010). Cortisol awakening response and hippocampal volume: vulnerability for major depressive disorder? *Biological Psychiatry* **68**, 847–853.

de Kloet ER, Derijk RH, Meijer OC (2007). Therapy insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nature Clinical Practice Endocrinology and Metabolism* **3**, 168–179.

de Kloet ER, Van Acker SA, Sibug RM, Oitzl MS, Meijer OC, Rahmouni K, de Jong W (2000). Brain mineralocorticoid receptors and centrally regulated functions. *Kidney International* **57**, 1329–1336.

DeRijk RH, de Kloet ER, Zitman FG, van Leeuwen N (2011). Mineralocorticoid receptor gene variants as determinants of HPA axis regulation and behavior. *Endocrine Development* **20**, 137–148.

Deuschle M, Schweiger U, Weber B, Gotthardt U, Korner A, Schmider J, Standhardt H, Lammers CH, Heuser I (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.

Dinan TG, Lavelle E, Cooney J, Burnett F, Scott L, Dash A, Thakore J, Berti C (1997). Dexamethasone augmentation in treatment-resistant depression. *Acta Psychiatrica Scandinavia* **95**, 58–61.

Dong HW, Swanson LW, Chen L, Fanselow MS, Toga AW (2009). Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1. *Proceedings of the National Academy of Sciences USA* **106**, 11794–11799.

Dougherty LR, Klein DN, Olino TM, Dyson M, Rose S (2009). Increased waking salivary cortisol and depression risk in preschoolers: the role of maternal history of melancholic depression and early child temperament. *Journal of Child Psychology and Psychiatry* **50**, 1495–1503.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry* **67**, 446–457.

Duman RS, Malberg J, Thome J (1999). Neural plasticity to stress and antidepressant treatment. *Biological Psychiatry* **46**, 1181–1191.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **112**, 257–269.

Engert V, Efanov SI, Dedovic K, Dagher A, Pruessner JC (2011). Increased cortisol awakening response and afternoon/evening cortisol output in healthy young adults with low early life parental care. *Psychopharmacology* (*Berlin*) **214**, 261–268.

Engert V, Efanov SI, Dedovic K, Duchesne A, Dagher A, Pruessner JC (2010). Perceived early-life maternal care and the cortisol response to repeated psychosocial stress. *Journal of Psychiatry and Neuroscience* **35**, 370–377.

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998). Neurogenesis in the adult human hippocampus. *Nature Medicine* **4**, 1313–1317.

Feldman D, Mondon CE, Horner JA, Weiser JN (1979). Glucocorticoid and estrogen regulation of corticosteroid-binding globulin production by rat liver. *Americal Journal of Physiology* **237**, E493–E499.

Flammer JR, Rogatsky I (2011). Minireview: Glucocorticoids in autoimmunity: unexpected targets and mechanisms. *Molecular Endocrinology* **25**, 1075–1086.

Flores BH, Kenna H, Keller J, Solvason HB, Schatzberg AF (2006). Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* **31**, 628–636.

Franz CE, O'Brien RC, Hauger RL, Mendoza SP, Panizzon MS, Prom-Wormley E, Eaves LJ, Jacobson K, Lyons MJ, Lupien S, Hellhammer D, Xian H, Kremen WS (2011). Cross-sectional and 35-year longitudinal assessment of salivary cortisol and cognitive functioning: the Vietnam Era twin study of aging. *Psychoneuroendocrinology* **36**, 1040–1052.

Gadek-Michalska A, Bugajski AJ, Bugajski J (2008). Prostaglandins and interleukin-1beta in the hypothalamic-pituitary-adrenal response to systemic phenylephrine under basal and stress conditions. *Journal of Physiology and Pharmacology* **59**, 563–575.

Garcia-Bueno B, Caso JR, Leza JC (2008). Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. *Neuroscience and Biobehavioral Reviews* **32**, 1136–1151.

Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, Gordon E, Kemp AH, Williams LM (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular Psychiatry* **14**, 681–695.

Gemma C, Bachstetter AD, Cole MJ, Fister M, Hudson C, Bickford PC (2007). Blockade of caspase-1 increases neurogenesis in the aged hippocampus. *European Journal of Neuroscience* **26**, 2795–2803.

Gerritsen L, Geerlings MI, Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Comijs HC (2009). Personality characteristics and hypothalamic-pituitary-adrenal axis regulation in older persons. *American Journal of Geriatric Psychiatry* **17**, 1077–1084.

Gilhooley MJ, Pinnock SB, Herbert J (2011). Rhythmic expression of per1 in the dentate gyrus is suppressed by corticosterone: implications for neurogenesis. *Neuroscience Letters* **489**, 177–181.

Glover V, O'Connor TG, O'Donnell K (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews* **35**, 17–22.

Goodwin GM, Muir WJ, Seckl JR, Bennie J, Carroll S, Dick H, Fink G (1992). The effects of cortisol infusion upon hormone secretion from the anterior pituitary and subjective mood in depressive illness and in controls. *Journal of Affective Disorders* **26**, 73–83.

Goodyer IM, Bacon A, Ban M, Croudace T, Herbert J (2009). Serotonin transporter genotype, morning cortisol and subsequent depression in adolescents. *British Journal of Psychiatry* **195**, 39–45.

Goodyer IM, Croudace T, Dudbridge F, Ban M, Herbert J (2010). Polymorphisms in BDNF (Val66Met) and 5-HTTLPR, morning cortisol and subsequent depression in at-risk adolescents. *British Journal of Psychiatry* **197**, 365–371.

Goodyer IM, Herbert J, Tamplin A (2003). Psychoendocrine antecedents of persistent first-episode major depression in adolescents: a community-based longitudinal enquiry. *Psychological Medicine* **33**, 601–610.

Goodyer IM, Herbert J, Tamplin A, Altham PM (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *British Journal of Psychiatry* **177**, 499–504.

Groves JO (2007). Is it time to reassess the BDNF hypothesis of depression? *Molecular Psychiatry* **12**, 1079–1088.

Guazzo EP, Kirkpatrick PJ, Goodyer IM, Shiers HM, Herbert J (1996). Cortisol, dehydroepiandrosterone

(DHEA), and DHEA sulfate in the cerebrospinal fluid of man: relation to blood levels and the effects of age. *Journal of Clinical Endocrinology and Metabolism* **81**, 3951–3960.

Gubba EM, Netherton CM, Herbert J (2000). Endangerment of the brain by glucocorticoids: experimental and clinical evidence. *Journal of Neurocytology* **29**, 439–449.

Gutierrez-Mecinas M, Trollope AF, Collins A, Morfett H, Hesketh SA, Kersante F, Reul JM (2011). Long-lasting behavioral responses to stress involve a direct interaction of glucocorticoid receptors with ERK1/2-MSK1-Elk-1 signaling. *Proceedings of the National Academy of Sciences USA* **108**, 13806–13811.

Hainer V, Kunesova M, Stunkard AJ, Parizkova J, Stich V, Mikulova R, Starka L (2001). The within-pair resemblance in serum levels of androgens, sex-hormone binding globulin and cortisol in female obese identical twins – effect of negative energy balance induced by very low-calorie diet. *Hormone and Metabolic Research* **33**, 417–422.

Halligan SL, Herbert J, Goodyer IM, Murray L (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. *Biological Psychiatry* **55**, 376–381.

Harris TO, Borsanyi S, Messari S, Stanford K, Cleary SE, Shiers HM, Brown GW, Herbert J (2000). Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *British Journal of Psychiatry* **177**, 505–510.

Hasler BP, Buysse DJ, Kupfer DJ, Germain A (2010). Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. *Psychiatry Research* **178**, 205–207.

Hastings MH, Maywood ES, Reddy AB (2008). Two decades of circadian time. *Journal of Neuroendocrinology* **20**, 812–819.

Hazra A, DuBois DC, Almon RR, Jusko WJ (2007). Assessing the dynamics of nuclear glucocorticoid-receptor complex: adding flexibility to gene expression modeling. *Journal of Pharmacokinetics and Pharmacodynamics* **34**, 333–354.

Herbert J (1993). Peptides in the limbic system: neurochemical codes for co-ordinated adaptive responses to behavioural and physiological demand. *Progress in Neurobiology* **41**, 723–791.

Herbert J, Goodyer IM, Grossman AB, Hastings MH, de Kloet ER, Lightman SL, Lupien SJ, Roozendaal B, Seckl JR (2006). Do corticosteroids damage the brain? *Journal of Neuroendocrinology* **18**, 393–411.

Het S, Wolf OT (2007). Mood changes in response to psychosocial stress in healthy young women: effects of pretreatment with cortisol. *Behavioral Neuroscience* **121**, 11–20.

Heydendael W, Jacobson L (2009). Glucocorticoid status affects antidepressant regulation of locus coeruleus tyrosine hydroxylase and dorsal raphe tryptophan hydroxylase gene expression. *Brain Research* **1288**, 69–78.

Holsboer F, Grasser A, Friess E, Wiedemann K (1994). Steroid effects on central neurons and implications for psychiatric and neurological disorders. *Annals of the New York Academy of Sciences* **746**, 345–359; discussion 359–361.

Homberg JR, Lesch KP (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry* **69**, 513–519.

Huang GJ, Herbert J (2006). Stimulation of neurogenesis in the hippocampus of the adult rat by fluoxetine requires rhythmic change in corticosterone. *Biological Psychiatry* **59**, 619–624.

Hucklebridge F, Clow A, Evans P (1998). The relationship between salivary secretory immunoglobulin A and cortisol: neuroendocrine response to awakening and the diurnal cycle. *International Journal of Psychophysiology* **31**, 69–76.

Hunter AL, Minnis H, Wilson P (2011). Altered stress responses in children exposed to early adversity: a systematic review of salivary cortisol studies. *Stress* **14**, 614–626.

Ivy AS, Rex CS, Chen Y, Dube C, Maras PM, Grigoriadis DE, Gall CM, Lynch G, Baram TZ (2010). Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *Journal of Neuroscience* **30**, 13005–13015.

Jeffcoate WJ, Silverstone JT, Edwards CR, Besser GM (1979). Psychiatric manifestations of Cushing's syndrome: response to lowering of plasma cortisol. *Quarterly Journal of Medicine* **48**, 465–472.

Joels M, de Kloet ER (1994). Mineralocorticoid and glucocorticoid receptors in the brain. Implications for ion permeability and transmitter systems. *Progress in Neurobiology* **43**, 1–36.

Kahl KG, Bens S, Ziegler K, Rudolf S, Dibbelt L, Kordon A, Schweiger U (2006). Cortisol, the cortisol-dehydroepiandrosterone ratio, and pro-inflammatory cytokines in patients with current major depressive disorder comorbid with borderline personality disorder. *Biological Psychiatry* **59**, 667–671.

Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G (2005). Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. *Biological Psychiatry* **57**, 1068–1072.

Karishma KK, Herbert J (2002). Dehydroepiandrosterone (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression. *European Journal of Neuroscience* **16**, 445–453.

Kathol RG, Jaeckle RS, Lopez JF, Meller WH (1989). Pathophysiology of HPA axis abnormalities in patients with major depression: an update. *American Journal of Psychiatry* **146**, 311–317.

Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S, Krystal JH, Gelernter J (2006). Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biological Psychiatry* **59**, 673–680.

Kendler KS, Kuhn JW, Prescott CA (2004). Childhood sexual abuse, stressful life events and risk for major depression in women. *Psychological Medicine* **34**, 1475–1482.

Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, Lozano AM (2011). Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *American Journal of Psychiatry* **168**, 502–510.

Khorram O, Vu L, Yen SS (1997). Activation of immune function by dehydroepiandrosterone (DHEA) in age-advanced men. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* **52**, M1–M7.

Kimonides VG, Khatibi NH, Svendsen CN, Sofroniew MV, Herbert J (1998). Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. *Proceedings of the National Academy of Sciences USA* **95**, 1852–1857.

Koenigsberg HW, Teicher MH, Mitropoulou V, Navalta C, New AS, Trestman R, Siever LJ (2004). 24-h Monitoring of plasma norepinephrine, MHPG, cortisol, growth hormone and prolactin in depression. *Journal of Psychiatric Research* **38**, 503–511.

Kohler S, Thomas AJ, Lloyd A, Barber R, Almeida OP, O'Brien JT (2010). White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. *British Journal of Psychiatry* **196**, 143–149.

Kunugi H, Hori H, Adachi N, Numakawa T (2010). Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. *Psychiatry and Clinical Neuroscience* **64**, 447–459.

Langenecker SA, Weisenbach SL, Giordani B, Briceno EM, Guidotti Breting LM, Schallmo MP, Leon HM, Noll DC, Zubieta JK, Schteingart DE, Starkman MN (2012). Impact of chronic hypercortisolemia on affective processing. *Neuropharmacology* **62**, 217–225.

Lenczowski MJ, Bluthe RM, Roth J, Rees GS, Rushforth DA, van Dam AM, Tilders FJ, Dantzer R, Rothwell NJ, Luheshi GN (1999). Central administration of rat IL-6 induces HPA activation and fever but not sickness behavior in rats. *American Journal of Physiology* **276**, R652–R658.

Lewis DA, Smith RE (1983). Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *Journal of Affective Disorders* **5**, 319–332.

Lewis G, Collishaw S, Harold G, Rice F, Thapar A (2012). Maternal depression and child and adolescent depression symptoms: an exploratory test for moderation by CRHR1, FKBP5 and NR3C1 gene variants. *Behavioral Genetics* **42**, 121–132.

Lightman SL, Conway-Campbell BL (2010). The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration. *Nature Reviews Neuroscience* **11**, 710–718.

Lightman SL, Wiles CC, Atkinson HC, Henley DE, Russell GM, Leendertz JA, McKenna MA, Spiga F, Wood SA, Conway-Campbell BL (2008). The significance of glucocorticoid pulsatility. *European Journal of Pharmacology* **583**, 255–262.

Liston C, Gan WB (2011). Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. *Proceedings of the National Academy of Sciences USA* **108**, 16074–16079.

Luby JL, Heffelfinger A, Mrakotsky C, Brown K, Hessler M, Spitznagel E (2003). Alterations in stress cortisol reactivity in depressed preschoolers relative to psychiatric and no-disorder comparison groups. *Archives of General Psychiatry* **60**, 1248–1255.

Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience* **10**, 434–445.

Maes M (2011). Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Progress in Neuropsychopharmacology and Biological Psychiatry* **35**, 664–675.

Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R (2011). The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Progress in Neuropsychopharmacology and Biological Psychiatry* **35**, 702–721.

Magarinos AM, McEwen BS (1995). Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience* **69**, 89–98.

Malberg JE (2004). Implications of adult hippocampal neurogenesis in antidepressant action. *Journal of Psychiatry and Neuroscience* **29**, 196–205.

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *Journal of Neuroscience* **20**, 9104–9110.

Mannie ZN, Harmer CJ, Cowen PJ (2007). Increased waking salivary cortisol levels in young people at familial risk of depression. *American Journal of Psychiatry* **164**, 617–621.

Markopoulou K, Papadopoulos A, Juruena MF, Poon L, Pariante CM, Cleare AJ (2009). The ratio of cortisol/DHEA in treatment resistant depression. *Psychoneuroendocrinology* **34**, 19–26.

Masters JN, Finch CE, Sapolsky RM (1989). Glucocorticoid endangerment of hippocampal neurons does not involve deoxyribonucleic acid cleavage. *Endocrinology* **124**, 3083–3088.

May M, Holmes E, Rogers W, Poth M (1990). Protection from glucocorticoid induced thymic involution by dehydroepiandrosterone. *Life Sciences* **46**, 1627–1631.

Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, Castren E, Maffei L (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science* **320**, 385–388.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005). Deep brain stimulation for treatment-resistant depression. *Neuron* **45**, 651–660.

Mayer EA, Baldi JP (1991). Can regulatory peptides be regarded as words of a biological language. *American Journal of Physiology* **261**, G171–G184.

Maywood ES, O'Neill J, Wong GK, Reddy AB, Hastings MH (2006). Circadian timing in health and disease. *Progress in Brain Research* **153**, 253–269.

Maywood ES, O'Neill JS, Reddy AB, Chesham JE, Prosser HM, Kyriacou CP, Godinho SI, Nolan PM, Hastings MH (2007). Genetic and molecular analysis of the central and peripheral circadian clockwork of mice. *Cold Spring Harbor Symposia in Quantitative Biology* **72**, 85–94.

McGowan PO, Suderman M, Sasaki A, Huang TC, Hallett M, Meaney MJ, Szyf M (2011). Broad epigenetic signature of maternal care in the brain of adult rats. *PLoS ONE* **6**, e14739.

McLaughlin KA, Nolen-Hoeksema S (2011). Rumination as a transdiagnostic factor in depression and anxiety. *Behavioral Research and Therapy* **49**, 186–193.

McMaster A, Jangani M, Sommer P, Han N, Brass A, Beesley S, Lu W, Berry A, Loudon A, Donn R, Ray DW (2011). Ultradian cortisol pulsatility encodes a distinct, biologically important signal. *PLoS ONE* **6**, e15766.

Meaney MJ, Szyf M (2005). Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues in Clinical Neuroscience* **7**, 103–123.

Menet JS, Rosbash M (2011). When brain clocks lose track of time: cause or consequence of neuropsychiatric disorders. *Current Opinion in Neurobiology* **21**, 1–9.

Merz CJ, Tabbert K, Schweckendiek J, Klucken T, Vaitl D, Stark R, Wolf OT (2010). Investigating the impact of sex and cortisol on implicit fear conditioning with fMRI. *Psychoneuroendocrinology* **35**, 33–46.

Michael A, Jenaway A, Paykel ES, Herbert J (2000). Altered salivary dehydroepiandrosterone levels in major depression in adults. *Biological Psychiatry* **48**, 989–995.

Mullen PE, Linsell CR, Parker D (1986). Influence of sleep disruption and calorie restriction on biological markers for depression. *Lancet* **2**, 1051–1055.

Nater UM, Hoppmann C, Klumb PL (2010). Neuroticism and conscientiousness are associated with cortisol diurnal profiles in adults – role of positive and negative affect. *Psychoneuroendocrinology* **35**, 1573–1577.

Nederhof E, Bouma EM, Oldehinkel AJ, Ormel J (2010). Interaction between childhood adversity, brain-derived neurotrophic factor val/met and serotonin transporter promoter polymorphism on depression: the TRAILS study. *Biological Psychiatry* **68**, 209–212.

Netherton C, Goodyer I, Tamplin A, Herbert J (2004). Salivary cortisol and dehydroepiandrosterone in relation to puberty and gender. *Psychoneuroendocrinology* **29**, 125–140.

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry* **56**, 527–533.

Nishi M, Noriko HH, Kawata M (2011). Intranuclear dynamics of corticosteroid receptors and effects of proteasomal activity in cultured hippocampal neural cells. *Neuroscience Letters* **494**, 65–69.

Nolen-Hoeksema S, Wisco EE, Lynubomirsky S (2011). Rethinking rumination. *Perpectives on Psychological Science* **3**, 400–424.

Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics* **3**, 97–106.

O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N (2004). A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *American Journal of Psychology* **161**, 2081–2090.

O'Regan D, Welberg LL, Holmes MC, Seckl JR (2001). Glucocorticoid programming of pituitary-adrenal function: mechanisms and physiological consequences. *Seminars in Neonatology* **6**, 319–329.

Orentreich N, Brind JL, Rizer RL, Vogelman JH (1984). Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *Journal of Clinical Endocrinology and Metabolism* **59**, 551–555.

Orentreich N, Brind JL, Vogelman JH, Andres R, Baldwin H (1992). Long-term longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. *Journal of Clinical Endocrinology and Metabolism* **75**, 1002–1004.

Otte C, Marmar CR, Pipkin SS, Moos R, Browner WS, Whooley MA (2004). Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: the Heart and Soul Study. *Biological Psychiatry* **56**, 241–247.

Ouellet-Morin I, Boivin M, Dionne G, Lupien SJ, Arseneault L, Barr RG, Perusse D, Tremblay RE (2008). Variations in heritability of cortisol reactivity to stress as a function of early familial adversity among 19-month-old twins. *Archives of General Psychiatry* **65**, 211–218.

Oxenkrug GF (2010). Tryptophan kynurenine metabolism as a common mediator of genetic and environmental impacts in major depressive disorder: the serotonin hypothesis revisited 40 years later. *Israeli Journal of Psychiatry and Related Sciences* **47**, 56–63.

Pace TW, Miller AH (2009). Cytokines and glucocorticoid receptor signaling. Relevance to major depression. *Annals of the New York Academy of Sciences* **1179**, 86–105.

Parker GB, Brown LB (1982). Coping behaviors that mediate between life events and depression. *Archives of General Psychiatry* **39**, 1386–1391.

Pereira AM, Tiemensma J, Romijn JA (2010). Neuropsychiatric disorders in Cushing's syndrome. *Neuroendocrinology* **92** (Suppl. 1), 65–70.

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neuroscience* **8**, 828–834.

Pfohl B, Sherman B, Schlechte J, Stone R (1985). Pituitary-adrenal axis rhythm disturbances in psychiatric depression. *Archives of General Psychiatry* **42**, 897–903.

Pinnock SB, Balendra R, Chan M, Hunt LT, Turner-Stokes T, Herbert J (2007). Interactions between nitric oxide and corticosterone in the regulation of progenitor cell proliferation in the dentate gyrus of the adult rat. *Neuropsychopharmacology* **32**, 493–504.

Pinnock SB, Blake AM, Platt NJ, Herbert J (2010). The roles of BDNF, pCREB and Wnt3a in the latent period preceding activation of progenitor cell mitosis in the adult dentate gyrus by fluoxetine. *PLoS ONE* **5**, e13652.

Piser TM (2010). Linking the cytokine and neurocircuitry hypotheses of depression: a translational framework for discovery and development of novel anti-depressants. *Brain, Behavior, and Immunology* **24**, 515–524.

Portella MJ, Harmer CJ, Flint J, Cowen P, Goodwin GM (2005). Enhanced early morning salivary cortisol in neuroticism. *American Journal of Psychiatry* **162**, 807–809.

Prickaerts J, van den Hove DL, Fierens FL, Kia HK, Lenaerts I, Steckler T (2006). Chronic corticosterone manipulations in mice affect brain cell proliferation rates, but only partly affect BDNF protein levels. *Neuroscience Letters* **396**, 12–16.

Qureshi AC, Bahri A, Breen LA, Barnes SC, Powrie JK, Thomas SM, Carroll PV (2007). The influence of the route of oestrogen administration on serum levels of cortisol-binding globulin and total cortisol. *Clinical Endocrinology* (*Oxford*) **66**, 632–635.

Rabkin JG, McElhiney MC, Rabkin R, McGrath PJ, Ferrando SJ (2006). Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *American Journal of Psychiatry* **163**, 59–66.

Reisch N, Arlt W (2009). Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinology and Metabolism Clinics of North America* **38**, 407–418, ix–x.

Reul JM, Gesing A, Droste S, Stec IS, Weber A, Bachmann C, Bilang-Bleuel A, Holsboer F, Linthorst AC (2000). The brain mineralocorticoid receptor: greedy for ligand, mysterious in function. *European Journal of Pharmacology* **405**, 235–249.

Roozendaal B, McEwen BS, Chattarji S (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience* **10**, 423–433.

Rosenfeld P, van Eekelen JA, Levine S, de Kloet ER (1993). Ontogeny of corticosteroid receptors in the brain. *Cellular and Molecular Neurobiology* **13**, 295–319.

Roskoden T, Otten U, Schwegler H (2004). Early postnatal corticosterone administration regulates neurotrophins and their receptors in septum and hippocampus of the rat. *Experimental Brain Research* **154**, 183–191.

Rubin RT, Phillips JJ, Sadow TF, McCracken JT (1995). Adrenal gland volume in major depression. Increase during the depressive episode and decrease with successful treatment. *Archives of General Psychiatry* **52**, 213–218.

Rush AJ, Giles DE, Schlesser MA, Orsulak PJ, Parker Jr. CR, Weissenburger JE, Crowley GT, Khatami M, Vasavada N (1996). The dexamethasone suppression test in patients with mood disorders. *Journal of Clinical Psychiatry* **57**, 470–484.

Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF (1973). Disrupted 24-hour patterns of cortisol secretion in psychotic depression. *Archives of General Psychiatry* **28**, 19–24.

Sairanen M, Lucas G, Ernfors P, Castren M, Castren E (2005). Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. *Journal of Neuroscience* **25**, 1089–1094.

Salomon S, Bejar C, Schorer-Apelbaum D, Weinstock M (2011). Corticosterone mediates some but not other behavioural changes induced by prenatal stress in rats. *Journal of Neuroendocrinology* **23**, 118–128.

Santos GM, Fairall L, Schwabe JW (2011). Negative regulation by nuclear receptors: a plethora of mechanisms. *Trends in Endocrinology and Metabolism* **22**, 87–93.

Sartorius A, Henn FA (2007). Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Medical Hypotheses* **69**, 1305–1308.

Schaaf MJ, de Jong J, de Kloet ER, Vreugdenhil E (1998). Downregulation of BDNF mRNA and protein in the rat hippocampus by corticosterone. *Brain Research* **813**, 112–120.

Schaaf MJ, Hoetelmans RW, de Kloet ER, Vreugdenhil E (1997). Corticosterone regulates expression of BDNF and trkB but not NT-3 and trkC mRNA in the rat hippocampus. *Journal of Neuroscience Research* **48**, 334–341.

Schlesser MA, Winokur G, Sherman BM (1980). Hypothalamic-pituitary-adrenal axis activity in depressive illness. Its relationship to classification. *Archives of General Psychiatry* **37**, 737–743.

Schmidt PJ, Daly RC, Bloch M, Smith MJ, Danaceau MA, St Clair LS, Murphy JH, Haq N, Rubinow DR (2005). Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Archives of General Psychiatry* **62**, 154–162.

Schommer NC, Kudielka BM, Hellhammer DH, Kirschbaum C (1999). No evidence for a close relationship between personality traits and circadian cortisol rhythm or a single cortisol stress response. *Psychological Reports* **84**, 840–842.

Schulkin J (2011). Evolutionary conservation of glucocorticoids and corticotropin releasing hormone: behavioral and physiological adaptations. *Brain Research* **1392**, 27–46.

Seckl JR, Holmes MC (2007). Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nature Clinical Practice in Endocrinology and Metabolism* **3**, 479–488.

Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS (2002). Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *Journal of Neuroscience* **22**, 3251–3261.

Simpson GM, El Sheshai A, Loza N, Kingsbury SJ, Fayek M, Rady A, Fawzy W (2005). An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *Journal of Clinical Psychiatry* **66**, 598–602.

Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA (2011). A pathophysiological framework of hippocampal

dysfunction in ageing and disease. *Nature Reviews Neuroscience* **12**, 585–601.

Soravia LM, de Quervain DJ, Heinrichs M (2009). Glucocorticoids do not reduce subjective fear in healthy subjects exposed to social stress. *Biological Psychology* **81**, 184–188.

Soravia LM, Heinrichs M, Aerni A, Maroni C, Schelling G, Ehlert U, Roozendaal B, de Quervain DJ (2006). Glucocorticoids reduce phobic fear in humans. *Proceedings of the National Academy of Sciences USA* **103**, 5585–5590.

Srinivasan V, Singh J, Pandi-Perumal SR, Brown GM, Spence DW, Cardinali DP (2010). Jet lag, circadian rhythm sleep disturbances, and depression: the role of melatonin and its analogs. *Advances in Therapy* **27**, 796–813.

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

Steckler T (2010). Developing small molecule nonpeptidergic drugs for the treatment of anxiety disorders: is the challenge still ahead? *Current Topics in Behavioral Neuroscience* **2**, 415–428.

Stranahan AM, Arumugam TV, Mattson MP (2011). Lowering corticosterone levels reinstates hippocampal brain-derived neurotropic factor and Trkb expression without influencing deficits in hypothalamic brain-derived neurotropic factor expression in leptin receptor-deficient mice. *Neuroendocrinology* **93**, 58–64.

Strelzyk F, Hermes M, Naumann E, Oitzl M, Walter C, Busch HP, Richter S, Schachinger H (2012). Tune it down to live it up? Rapid, nongenomic effects of cortisol on the human brain. *Journal of Neuroscience* **32**, 616–625.

Sun CL, Francisco L, Baker KS, Weisdorf DJ, Forman SJ, Bhatia S (2011). Adverse psychological outcomes in long-term survivors of hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood* **118**, 4723–4731.

Szyf M, Weaver IC, Champagne FA, Diorio J, Meaney MJ (2005). Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. *Frontiers in Neuroendocrinology* **26**, 139–162.

Tiemensma J, Biermasz NR, Middelkoop HA, van der Mast RC, Romijn JA, Pereira AM (2010). Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease. *Journal of Clinical Endocrinology and Metabolism* **95**, E129–E141.

Tombaugh GC, Yang SH, Swanson RA, Sapolsky RM (1992). Glucocorticoids exacerbate hypoxic and hypoglycemic hippocampal injury in vitro: biochemical correlates and a role for astrocytes. *Journal of Neurochemistry* **59**, 137–146.

Turner JD, Alt SR, Cao L, Vernocchi S, Trifonova S, Battello N, Muller CP (2010). Transcriptional control of the glucocorticoid receptor: CpG islands, epigenetics and more. *Biochemical Pharmacology* **80**, 1860–1868.

Tyrka AR, Kelly MM, Graber JA, DeRose L, Lee JK, Warren MP, Brooks-Gunn J (2010). Behavioral adjustment in a community sample of boys: links with basal and stress-induced salivary cortisol concentrations. *Psychoneuroendocrinology* **35**, 1167–1177.

Uchida Y, Ohtsuki S, Kamiie J, Terasaki T (2011). Blood-brain barrier (BBB) pharmacoproteomics (PPx): reconstruction of in vivo brain distribution of 11 P-glycoprotein substrates based on the BBB transporter protein concentration, in vitro intrinsic transport activity, and unbound fraction in plasma and brain in mice. *Journal of Pharmacology and Experimental Therapeutics* **339**, 579–588.

Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, Holden J (1994). Neurotoxicity of glucocorticoids in the primate brain. *Hormones and Behavoir* **28**, 336–348.

van der Meer MJ, Hermus AR, Pesman GJ, Sweep CG (1996). Effects of cytokines on pituitary beta-endorphin and adrenal corticosterone release in vitro. *Cytokine* **8**, 238–247.

van der Vegt EJ, van der Ende J, Huizink AC, Verhulst FC, Tiemeier H (2010). Childhood adversity modifies the relationship between anxiety disorders and cortisol secretion. *Biological Psychiatry* **68**, 1048–1054.

van Rossum EF, Russcher H, Lamberts SW (2005). Genetic polymorphisms and multifactorial diseases: facts and fallacies revealed by the glucocorticoid receptor gene. *Trends in Endocrinology and Metabolism* **16**, 445–450.

van Rossum EF, van den Akker EL (2011). Glucocorticoid resistance. *Endocrine Development* **20**, 127–136.

van Santen A, Vreeburg SA, Van der Does AJ, Spinhoven P, Zitman FG, Penninx BW (2011). Psychological traits and the cortisol awakening response: results from the Netherlands Study of Depression and Anxiety. *Psychoneuroendocrinology* **36**, 240–248.

Veen G, van Vliet IM, DeRijk RH, Giltay EJ, van Pelt J, Zitman FG (2010). Basal cortisol levels in relation to dimensions and DSM-IV categories of depression and anxiety. *Psychiatry Research* **185**, 121–128.

Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vasquez A, Buitelaar JK, Franke B (2010). Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. *Molecular Psychiatry* **15**, 260–271.

von Zerssen D, Barthelmes H, Dirlich G, Doerr P, Emrich HM, von Lindern L, Lund R, Pirke KM (1985). Circadian rhythms in endogenous depression. *Psychiatry Research* **16**, 51–63.

Vreeburg SA, Hartman CA, Hoogendijk WJ, van Dyck R, Zitman FG, Ormel J, Penninx BW (2010). Parental history of depression or anxiety and the cortisol awakening response. *British Journal of Psychiatry* **197**, 180–185.

Wachtel SR, de Wit H (2001). Lack of effect of intravenous hydrocortisone on mood in humans: a preliminary study. *Behavioral Pharmacology* **12**, 373–376.

Watanabe Y, Gould E, McEwen BS (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Research* **588**, 341–345.

White T, Ozel B, Jain JK, Stanczyk FZ (2006). Effects of transdermal and oral contraceptives on estrogen-sensitive hepatic proteins. *Contraception* **74**, 293–296.

Wichers MC, Myin-Germeys I, Jacobs N, Kenis G, Derom C, Vlietinck R, Delespaul P, Mengelers R, Peeters F, Nicolson N, van Os J (2008). Susceptibility to depression expressed as alterations in cortisol day curve: a cross-twin, cross-trait study. *Psychosomatic Medicine* **70**, 314–318.

Wiench M, John S, Baek S, Johnson TA, Sung MH, Escobar T, Simmons CA, Pearce KH, Biddie SC, Sabo PJ, Thurman RE, Stamatoyannopoulos JA, Hager GL (2011). DNA methylation status predicts cell type-specific enhancer activity. *EMBO Journal* **30**, 3028–3039.

Wirth MM, Scherer SM, Hoks RM, Abercrombie HC (2011). The effect of cortisol on emotional responses depends on order of cortisol and placebo administration in a within-subject design. *Psychoneuroendocrinology* **36**, 945–954.

Wirz-Justice A (2006). Biological rhythm disturbances in mood disorders. *International Clinical Psychopharmacology* **21** (Suppl. 1), S11–S15.

Wolf OT, Convit A, McHugh PF, Kandil E, Thorn EL, De Santi S, McEwen BS, de Leon MJ (2001). Cortisol differentially affects memory in young and elderly men. *Behavioral Neuroscience* **115**, 1002–1011.

Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E (1999). Double-blind treatment of major depression with dehydroepiandrosterone. *American Journal of Psychiatry* **156**, 646–649.

Wong EY, Herbert J (2004). The corticoid environment: a determining factor for neural progenitors' survival in the adult hippocampus. *European Journal of Neuroscience* **20**, 2491–2498.

Wong EY, Herbert J (2006). Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. *Neuroscience* **137**, 83–92.

Yang S, Liu A, Weidenhammer A, Cooksey RC, McClain D, Kim MK, Aguilera G, Abel ED, Chung JH (2009). The role of mPer2 clock gene in glucocorticoid and feeding rhythms. *Endocrinology* **150**, 2153–2160.

Young EA, Carlson NE, Brown MB (2001). Twenty-four-hour ACTH and cortisol pulsatility in depressed women. *Neuropsychopharmacology* **25**, 267–276.

Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H (2003). Mineralocorticoid receptor function in major depression. *Archives of General Psychiatry* **60**, 24–28.

Young EA, Nolen-Hoeksema S (2001). Effect of ruminations on the saliva cortisol response to a social stressor. *Psychoneuroendocrinology* **26**, 319–329.

Zamudio SR, Quevedo-Corona L, Garces L, De La Cruz F (2009). The effects of acute stress and acute corticosterone administration on the immobility response in rats. *Brain Research Bulletin* **80**, 331–336.

Zimmermann P, Bruckl T, Nocon A, Pfister H, Binder EB, Uhr M, Lieb R, Moffitt TE, Caspi A, Holsboer F, Ising M (2011). Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study. *American Journal of Psychiatry* **168**, 1107–1116.

Zoccola PM, Quas JA, Yim IS (2010). Salivary cortisol responses to a psychosocial laboratory stressor and later verbal recall of the stressor: the role of trait and state rumination. *Stress* **13**, 435–443.

Zunszain PA, Anacker C, Cattaneo A, Choudhury S, Musaelyan K, Myint AM, Thuret S, Price J, Pariante CM (2012). Interleukin-1beta: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology* **37**, 939–949.