Stress Hormone-Related Psychopathology: Pathophysiological and Treatment Implications

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Pathophysiological and Treatment Implications

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Summary
Stress is commonly associated with a variety of psychiatric conditions, including major depression, and with chronic medical conditions, including diabetes and insulin resistance. Whether stress causes these conditions is uncertain, but plausible mechanisms exist by which such effects might occur. To the extent stress-induced hormonal alterations (e.g., chronically elevated cortisol levels and lowered dehydroepiandrosterone [DHEA] levels) contribute to psychiatric and medical disease states, manipulations that normalize these hormonal aberrations should prove therapeutic. In this review, we discuss mechanisms by which hormonal imbalance (discussed in the frameworks of "allostatic load" and "anabolic balance") might contribute to illness. We then review certain clinical manifestations of such hormonal imbalances and discuss pharmacological and behavioural treatment strategies aimed at normalizing hormonal output and lessening psychiatric and physical pathology.

Key Words: stress, allostasis, depression, memory, hippocampus, Cushing's Syndrome, dehydroepiandrosterone (DHEA), cortisol, neurosteroids, BDNF, antigluocorticoid, Metabolic Syndrome, visceral obesity.

Introduction
"We are on our guard against external intoxicants, but hormones are parts of our bodies; it takes more wisdom to recognize and overcome the foe who fights from within. . . . (But) what can we do about this? . . . We do not yet know enough about their workings to justify any attempt at regulating our emotional key by taking hormones." - The Stress of Life (Selye 1956)

Forty-five years after Hans Selye, the "Father of Stress Physiology," wrote these words, we are seemingly in a much stronger position to "regulate our emotional key" by recognizing and correcting hormonal imbalances that are associated with behavioural disturbances. In this review, we attempt to summarize our current understanding of the relationship of stress and stress hormone dysregulation to psychiatric disorders and to certain health outcomes, and we speculate on the role of novel hormonal interventions in treating such disorders. We specifically address the following questions: (1) Do alterations in stress hormones directly contribute to psychopathology? (2) Do these changes in stress hormones also contribute to the high comorbidity between depression and certain chronic diseases? (3) If so, what are the mechanisms of these effects? (4) How are these effects manifest in clinical settings? (5) Can beneficial effects accrue from treatment strategies primarily aimed at normalizing stress hormone activity? (6) Which specific treatment strategies hold promise in this regard? Pharmacological treatment strategies are our primary focus here, but we also review evidence suggesting that certain behavioural interventions have comparable effects, perhaps via similar endocrinological mechanisms. While our primary emphasis in this review is the relationship of stress hormones to depression and cognition, we also consider alterations in energy metabolism (e.g., visceral obesity, eating and insulin resistance) as a somatic example of a network of regulatory systems that is directly affected by stress and that commonly becomes disturbed in psychiatric illness. Understanding common causes for depression and metabolic dysregulation could provide insight into effective treatments for people with this comorbidity.

Stress responses, allostatic load and anabolic balance

• Acute stress
When stress is acute, adaptive biochemical responses include increased adrenocortical secre-
tion of stress hormones, prominently cortisol and dehydroepiandrosterone (DHEA). Glucocorticoid secretion (specifically, cortisol in humans, corticosterone in many animal species) increases appetite, antagonizes insulin's cellular actions (thereby inhibiting further glucose storage), stimulates glycogenolysis and gluconeogenesis, breaks down protein stores and redistributes fatty acids from fat stores into the circulation to make energy more readily available to muscle tissue; this facilitates muscles' ability to respond robustly to imminent threat. Stress-induced cortisol surges also focus attention, arousal and alertness, increase vascular tone and blood pressure, demarginate white blood cells from the vascular linings into the circulation and temporarily suppress "unnecessary" bodily functions such as digestion, bone growth, wound repair and reproduction. The role of concomitant DHEA secretion in the acute stress response is less clear, but it has anabolic effects and may serve to buffer the organism from excessive cortisol activity due to DHEA's intrinsic "anti-gluocorticoid" effects (Browne et al 1992; Hechter et al 1997; Hu et al 2000; Kalimi et al 1994; Leblhuber et al 1992; Patchev and Almeida 1997; Wolkowitz et al 1992). Under chronic stress, however, DHEA levels decline, and thus the ability to counteract the catabolic effects of glucocorticoids becomes impaired.

- **Allostasis**

  The role of glucocorticoids in the adaptive acute response to stress has been divided into separate classes of action that have differing time domains in response to the stressful stimulus (Sapolsky et al 2000). Permissive actions are those exerted by glucocorticoids prior to the onset of stress and tonically involved in the mediation of the initial response. Stimulatory and suppressive actions induced by glucocorticoids either enhance or inhibit the effects of the initial phasic change in stress responsive hormones, while preparative actions alter the physiological responses of the organism to the presentation of a subsequent stressor. In general, permissive actions are regulated by the mineralocorticoid ("Type 1") receptor (MR) at lower free cortisol or corticosterone concentrations. Stress-induced increases in cortisol or corticosterone output tend to result in a shift to suppressive actions (e.g., glucocorticoid negative feedback) mediated by the glucocorticoid ("Type 2") receptor (GR) (De Kloet et al 1998; Plihal et al 1996).

  Acute adrenocortical responses are critical for successful adaptation to stress, and, indeed, for life itself. However, when these responses are excessive or are extended for long periods of time, as in tonic activation of the GR, detrimental effects on both emotional well-being and physical health may ensue (McEwen 2000a; McEwen and Stellar 1993; McEwen et al 1992; Raber 1998; Seeman et al 1997; Sterling and Eyre 1988). Successful adaptation to stress has been termed "allostasis" (as opposed to "homeostasis") to reflect the fact that organisms must be facile in meeting the energetic and other demands of acutely stressful situations in a dynamic way and must, likewise, be able to restrain stress reactions when acute stressors subside (Sterling and Eyre 1988).

- **Allostatic load and anabolic balance**

  The excessive "wear and tear" associated with prolonged or inappropriate stress responses has been termed "allostatic load" (McEwen and Stellar 1993). Notably, under long-term stress, DHEA secretion decreases to below baseline levels while cortisol levels frequently remain elevated, rendering the individual especially vulnerable to the detrimental, unopposed effects of prolonged cortisol exposure. Framed in complementary terms, cortisol exerts prominent catabolic effects in the body (i.e., breakdown of metabolic compounds to produce energy); these can be adaptive acutely but can destroy essential tissue and function if left unchecked for long periods of time. DHEA (and other hormones such as growth hormone, testosterone and insulin-like growth factor [IGF-1]) have anabolic effects (i.e., promoting growth and repair) thus repairing catabolic damage so long as their levels remain sufficiently high in the circulation (Sterling and Eyre 1988). This understanding of the relationship between anabolic hormones, such as DHEA, testosterone and growth hormone, and catabolic hormones, such as cortisol, has led to the recent introduction of the term "anabolic balance" to highlight the importance of the ratio of anabolic-to-catabolic activity in determining health and well-being (Wolkowitz, O., Epel, E., & Reus, V. (2001). Anti-gluocorticoid strategies in treating major depression and health outcome. In T. Jorgin (Ed.), The Physical Consequences of Depression (pp. 181-212). Petersfield, UK: Wrightson Biomedical Publishing.). A low anabolic balance (e.g., low DHEA and/or high cortisol) is thought to be a primary response to chronic stress that leads to a cascade of dysregulation across systems and allostatic load (Barbieri et al 2001; Christeef et al 2000; Epel et al 1998; Goodyer et al 1996; Hechter et al 1997; Herbert 1997; Herbert 1998; Matoulek et al 2000; McEwen 1998; McEwen and Seeman 1999; Wolkowitz and Reus 2000; Seeman et al 2001), contributing to depression and certain chronic diseases. Relevant to the primary thesis of this review, failure to hormonally "adapt" to repeated or persistent stressors with normalization of adrenocortical output and of anabolic:catabolic balance may be a heuristically useful model of depression and other illnesses in humans (c.f. (Kennett et al 1985)). Catabolic vs. anabolic effects on glucose disposition provide a unifying theme for explaining the consequences discussed here of chronic glucocorticoids on both brain and body. In the brain, glucocorticoid inhibition of hippocampal glucose transport (which occurs at stress levels of glucocorticoids) (de Leon et al 1997) likely contributes to hippo-
campal neuronal endangerment (Sapolsky et al 2000; Sapolsky et al 1990; Sapolsky 1993; Sapolsky 1994). In the periphery, chronic exposure to elevated levels of glucocorticoids may result in insulin resistance, hyperinsulinaemia, hyperglycaemia and visceral adiposity, which are major components of the "Metabolic Syndrome X." (Bjorntorp et al 1999a; Matoulek et al 2000; Raber 1998). Additional components of this syndrome include hyperlipidaemia, hypertension, and other factors leading to disordered fat metabolism (Reaven 1994). In turn, the Metabolic Syndrome X is a risk factor for diabetes and cardiovascular disease (Reaven 1994).

Allostatic load is also thought to precede the expression of certain diagnosable chronic diseases (McEwen and Seeman 1999; Ericsen et al 1999). The concept of allostatic load has only been tested in preliminary ways so far. To date, allostatic load markers have included a composite index of markers reflecting regulation across multiple systems - high cortisol, catecholamines, cholesterol and blood pressure, poor blood sugar control, visceral fat deposition and low DHEA sulphate (DHEA-S). In the MacArthur Successful Aging Study, this index predicted declines in cognitive function (memory, spatial ability, abstract reasoning) and physical ability, the development of hypertension, diabetes and cardiovascular disease (stroke and heart attacks) in 1189 elderly people 2.5 years later (Seeman et al 1997), and of mortality and cognitive decline seven years later (Seeman et al 2001). Most striking, what appear to be subtle and subclinical signs of dysregulation may be pathophysiological. For example, relatively higher levels of stress mediators, such as cortisol and catecholamines, rather than clinically abnormal levels, confer risk of disease (McEwen 2000a; Seeman et al 1997; Seeman et al 2001). Seeman and colleagues created a separate composite measure of stress mediators (high levels of cortisol and catecholamines, and low levels of DHEA-S), which can be considered an index of anabolic balance, and compared it to a composite of more traditional risk factors for cardiovascular disease processes (visceral fat, blood pressure, hemoglobin glycosylation and blood lipids) (Seeman et al 2001). The stress mediators were equally predictive of mortality and declines in physical functioning, supporting the importance of anabolic balance in contributing to physical decline and disease processes, although the stress mediators did not significantly predict cognitive decline (Seeman et al 2001).

Glucocorticoid hormone mechanisms of action

- Central nervous system effects

Genomic effects: neurotransmitters and neuropeptides

The central nervous system (CNS) effects of stress and glucocorticoids are ultimately mediated by the neurotransmitter, neuropeptide, neurosteroid and neurotrophin actions described in this section. Glucocorticoids may impact the brain and behaviour by at least three mechanisms: genomic, non-genomic and neurotrophic or neurotoxic. Glucocorticoids freely cross neuronal cell membranes and, in neurons containing specific cytoplasmic steroid receptors, translocate as a steroid-receptor complex to the cell nucleus (De Kloet et al 1998; McEwen et al 1979). Neurons and astrocytes containing corticosteroid-specific receptors are densely located in the hippocampus, septum and amygdala (McEwen et al 1979), parts of the brain believed to be intimately involved in behaviour, mood, learning and memory (Xu et al 1998). The prefrontal cortex is likely also a behaviourally-relevant target of glucocorticoids (Lupien and McEwen 1997; Rajkowska 2000). In these brain regions, steroids regulate transcription of genes, such as those controlling neuropeptide, G-protein, neurotransmitter and neurotransmitter receptor synthesis and metabolism (De Kloet et al 1998; McEwen et al 1979; McEwen 1987; Biegon 1990; Chauloff 1993; Curzon 1994; Lesch and Lerer 1991; Lopez et al 1998; McEwen 1968; McEwen et al 1979; Price et al 1997; Schatzberg et al 1985; Slotkin et al 1996; Wolkowitz 1994; Wolkowitz et al 1990b; Wolkowitz et al 1997a). For example, glucocorticoids may decrease (or, in some cases, increase) norepinephrine (NE) levels (Wolkowitz et al 1987a; McEwen et al 1979; McEwen 1987) and alter the synthesis of a, and b-adrenergic receptors as well as the sensitivity of NE receptor-coupled adenylylate cyclase (De Kloet et al 1998). Such actions in the noradrenergic system may counteract antidepressant drug effects on b-adrenergic receptor responsiveness (Holboier and Barden 1996). Corticosteroids also increase brain regional dopamine turnover. This effect may be especially important in the pathophysiology of psychotic depression, a condition associated with significantly elevated cortisol levels (Schatzberg et al 1985; Wolkowitz et al 1986; Wolkowitz et al 1989; Wolkowitz et al 1987a) and in the pathophysiology of stimulant drug abuse (Goeders 1997; Piazza and Le Moal 1996).

In addition, glucocorticoids significantly alter serotonin (5HT) activity and regulate the synthesis of 5HT, receptors (Meijer et al 1997; Lopez et al 1998). Glucocorticoid effects on 5HT function are very complex but likely play a prominent role in regulating affect and vegetative function (Biegon 1990; Chauloff 1993; Curzon 1994; Joels et al 1997; Lopez et al 1998; Maes and Meltzer 1995; Price et al 1997; Slotkin et al 1996; Meijer et al 1997; McEwen 1987). Kennett and colleagues (Kennett et al 1985) noted that stressed rats developed increased corticosterone secretion, decreased hippocampal 5HT, receptor mRNA levels and increased "depressive" behaviours such as decreased locomotion, decreased open-field behaviour and anorexia. After S-7
days of stress exposure, however, the rats showed a normalization of corticosterone levels, SHT₁ receptor activity and behaviour. These presumably "adaptive" responses in SHT₁ receptor activity and behaviour were curtailed by repeated corticosterone injections but were facilitated by the corticosterone synthesis inhibitor, metyrapone, suggesting that persistently elevated glucocorticoid levels decrease adaptive responses in an animal model of depression. In the same experimental paradigm, female rats showed relatively increased corticosterone responses to stress, relatively decreased SHT₁ receptor function and relatively decreased behavioural adaptation to chronic stress, compared to male rats. However, when their heightened endogenous corticosterone response was inhibited with the antiglucocorticoid drug metyrapone, their serotonergic and behavioural responses became similar to those of the males (Haleem et al 1988). This latter finding may help explain the higher incidence of depression in females (Haleem et al 1988). Healy et al (Healy et al 1999) have also shown "antidepressant" effects of metyrapone in animal models and have suggested that such effects are related to treatment-induced changes in SHT₁ receptor function. Consistent with the notion of "anabolic balance" described above, Flugge et al (Flugge et al 1998) found that administration of testosterone to chronically stressed male tree shrews reversed certain "depressive" behaviours and normalized (i.e., increased) hippocampal SHT₁ receptors, despite cortisol levels remaining high, suggesting that a balance between glucocorticoids and androgens is important in maintaining normal numbers of these monoamine receptors. Experimental data on serotonergic mediation of antiglucocorticoid effects in humans are reviewed below. Cumulatively, such findings are consistent with the hypotheses of depressogenic effects of chronic hypercortisolemia (or of catabolic/anabolic imbalance) and possible antidepressant effects of antiglucocorticoid drugs.

Non-genomic effects: neurosteroids

In addition to genomically-mediated effects, certain steroids (e.g., "neurosteroids") interact directly (non-genomically) with neuronal cell surface receptors (e.g., the GABA<sub>A</sub> and NMDA receptors (Majewska 1987)). The steroid metabolic pathway, highlighting known neurosteroid hormones, is presented in Figure 1. The cell surface receptor-related effects of neurosteroids are bi-directional, with certain steroid metabolites having excitatory, and others having inhibitory effects (Majewska 1987; Starkman 1998). Although the vast majority of endocrinological studies in depression have focused on cortisol, changes in adrenal, gonadal or CNS synthesis of other steroid hormones, such as the neurosteroids, DHEA or DHEA sulphate (together abbreviated "DHEA(S)"), tetrahydroxy-corticosterone (THDOC), androsterone, pregnenolone sulphate and allopregnanolone (all of which possess agonist or antagonist activity at brain GABA<sub>A</sub> and other receptors), may prove equally if not more important for maintenance

Figure 1
Schematic pathway of steroid and neurosteroid biosynthesis and metabolism. The neurosteroids discussed in this review article are indicated in boxes.

Morphological effects: neurotoxicity, neuroendangerment and neuroprotection

Finally, chronic exposure of animals to stress or to high levels of glucocorticoids can induce morphological changes, such as decreased dendritic length and decreased apical dendritic branching, and even contribute to cell death in certain vulnerable neurons, e.g., hippocampal CA1 and CA3 neurons (Sapolsky et al. 1986; Virgin Jr et al. 1991; Souza et al. 2000), although glucocorticoids may have trophic effects in certain hippocampal subfields (McEwen et al. 1992). Sapolsky (Sapolsky 1996) and McEwen (McEwen 2000b) have elaborated several mechanisms through which glucocorticoids can directly damage hippocampal neurons or increase their vulnerability to damage. By impairing hippocampal cell glucose uptake, glucocorticoids may induce an energetic crisis, setting into motion a cascade of excitatory amino acid and calcium neurotoxicity as well as oxidative stress (Behl et al. 1997), thereby augmenting the effects of ongoing or coincident metabolic or neurological insults ("neuroendangerment"), such as ischemia, seizures, head trauma and hypoglycemia (Sapolsky 2000b). In the presence of excessive glucocorticoid levels, glutamate release is increased (McEwen 2000b; Venero and Borrell 1999) as is NMDA receptor binding (Mangat et al. 1998). Additionally, the calcium influx into hippocampal neurons is increased (Nair et al. 1998), and calcium's destructive effects are amplified (Elliott et al. 1993). Neuronal damage by these mechanisms is likely further exacerbated by decreased astrocytic survival, since astrocytes play an important role in facilitating neuronal glucose uptake and in removing damaging levels of glutamate from the synapse (Virgin Jr et al. 1991). Cumulatively, such events may prove directly neurotoxic even in the absence of extraneous insults.

Recently, an additional possible mechanism of neurotoxicity has been explored. Neurogenesis (the birth of new neurons) continues into adulthood in the dentate gyrus of the hippocampus (Gould and Tanapat 1999) as well as in the neocortex (Gould et al. 1999). Stress and excessive glucocorticoid exposure decrease brain expression of brain-derived neurotrophic factor (BDNF); this process has been hypothesized to contribute to hippocampal damage by inhibiting cell proliferation in the dentate gyrus and to play a causal role in the development of major depression and cognitive dysfunction (Duman et al. 1997; Gould and Tanapat 1999; Manji et al. 2000; Jacobs et al. 2000). Strategies that directly lower glucocorticoid levels, including adrenalectomy, increase hippocampal expression of BDNF mRNA (Grundy et al. 2000), although they do not fully abolish the ability of stress to decrease BDNF levels (Smith et al. 1995). Stress-induced neurotoxicity, therefore, seems multifactorial and only partially due to increased glucocorticoid exposure (Souza et al. 2000; Ohl et al. 2000). Reducing glucocorticoid levels facilitates neurogenesis, even in aged animals, and results in increased numbers of hippocampal granule cells (Cameron and McKay 1999). Glutamate antagonists, such as MK-801, also enhance neurogenesis, while glutamate analogs inhibit it (Gould et al. 1994).

As mentioned above, DHEA physiologically antagonizes certain of the deleterious effects of chronic cortisol or corticosterone exposure and, in addition, protects hippocampal tissue (Bastianetto et al. 1999; Cardounel et al. 1999; Kimonides et al. 1998; Kimonides et al. 1999; Mao and Barger 1998) and enhances hippocampal function (Murialdo et al. 2000). Indeed, in normal aging and in Alzheimer’s disease, hippocampal perfusion (Murialdo et al. 2000) and volume (Magri et al. 2000) are positively related to serum DHEAS levels and to the DHEAS/cortisol ratio. Mechanisms proposed for DHEA’s putative neuroprotective effects include: interactions with GABA, NMDA and sigma receptors, changes in brain regional serotonin and dopamine levels, increases in hippocampal primed burst potentiation and cholinergic function, decreases in hippocampal nuclear glucocorticoid receptor levels, decreases in the production and deposition of amyloid β protein, inhibition of the production of pro-inflammatory cytokines (e.g., IL-1-alpha, IL-6, and TNF-alpha), scavenging of free radicals, prevention of oxidative damage and increases in bioavailable levels of IGF-1 (Bastianetto et al. 1999; Cardounel et al. 1999; Kimonides et al. 1998; Kimonides et al. 1999; Mao and Barger 1998; Murialdo et al. 2000). These mechanisms are reviewed elsewhere (Wolkowitz and Reus 2000; Wolkowitz et al. 2000a; Wolkowitz et al. 2000c). Of particular interest, DHEA protects hippocampal neurons from glutamate toxicity, at least in part, by decreasing the nuclear localization of glucocorticoid receptors (GR) induced by glutamate treatment (Cardounel et al. 1999). Anabolic hormones other than DHEA can also have actions opposite to those seen with chronic glucocorticoid exposure. IGF-1, for example, increases hippocampal glucose utilization in aged animals (Lynch et al. 2001) and increases adult hippocampal neurogenesis (Aberg et al. 2000; Trejo et al. 2001). Testosterone also enhances survival of new neurons in the adult canary brain; this is likely effected by an increase in brain BDNF levels (Råska et al. 1999).

Chronic antidepressant or mood stabilizer treatment also opposes many of the adverse cellular
events caused by stress or chronic glucocorticoid exposure (Duman et al. 1997; Manji et al. 2000; Jacobs et al. 2000). Antidepressant treatment, in animals, has been found to increase neurogenesis in rat hippocampus (Malberg et al. 2000), to increase hippocampal expression of BDNF and to completely block the down-regulation of hippocampal BDNF mRNA that occurs in response to stress (Nibuya et al. 1995). Actions at the 5HT1 receptor seem particularly important in regulating hippocampal neurogenesis; nonetheless, both serotonergic and noradrenergic antidepressants increase neurogenesis and BDNF expression and prevent stress-induced down-regulation of 5HT1 receptors (Jacobs et al. 2000; Jacobs et al. 1998; Lopez et al. 1998). Antidepressant treatment also decreases intracellular calcium concentrations via inhibition of voltage-gated calcium channels (Deak et al. 2000) and thus would be expected to interfere with the glutamate-calcium neurotoxic cascade described above (Takebayashi et al. 2000; Sapolsky 2000b). Antidepressants may also dampen glutamatergic neurotoxicity by decreasing glutamate concentrations in prefrontal cortex (Michael-Titus et al. 2000) and caudate (Rosenberg et al. 2000) and by decreasing group I metabotropic glutamate receptor responsiveness in the hippocampus (Zahorodna and Bijak 1999). Cumulatively, such data suggest that chronic antidepressant treatment can exert neuroprotective effects in the face of stress or major depression (Michael-Titus et al. 2000). Such neuroprotective effects may represent previously unrecognized mechanisms of therapeutic action in treating depression and anxiety disorders (Rosenberg et al. 2000; Zahorodna and Bijak 1999; Jacobs et al. 2000). A simplified, theoretical model of the relationship between stress, major depression, antidepressants, corticosteroid activity, neurotransmitter activity, neurotrophin expression and hippocampal cell viability is presented in Figure 2.

Data suggesting neurotoxic or neuroendangering effects of glucocorticoids derive principally from studies with rodents, and it is uncertain to which extent they are applicable to humans and other primates. In a prospective study in Macaques examining hippocampal cell number at autopsy, administration of 3-6 mg/kg/day of hydrocortisone for 12 months could not be distinguished from placebo (Leverenz et al. 1999). However, chronically stressed vervet monkeys did show loss of hippocampal neurons, probably secondary to increased glucocorticoid exposure (Uno et al. 1989). These observations suggest that, at least in non-human primates, chronically elevated glucocorticoid concentrations are more likely to produce hippocampal neuronal damage under stressful than under non-stressful conditions (Sapolsky 2000a; Souza et al. 2000), perhaps because chronic stress evokes other biochemical changes which have synergistic effects on neurotoxicity and neuroendangerment (Herbert 1997; Herbert 1998; Souza et al. 2000). Data from a number of human populations, including patients with major depression, Alzheimer's disease, post-traumatic stress disorder and Cushing's syndrome, are consistent with the possibility that prolonged exposure to elevated cortisol levels leads to decreased hippocampal volume (Bremner 1999; Herbert 1998; McEwen 2000c; O'Brien et al. 1996; Sapolsky 2000a; Sapolsky 2000b; Sheline et al. 1999; Starkman et al. 1992) and to impaired hippocampus-dependent memory function (Lupien et al. 1999; Starkman et al. 1992; Newcomer et al. 1999). The diminished hippocampal volume observed in Cushing's syndrome seems (at least partially) reversible with normalization of glucocorticoid status (Starkman et al. 1999), but in some cases, areas of brain damage may be irreversible or only partially reversible (Trethowan and Cobb 1952). Hippocampal volume loss seen in patients with extensive past histories of major depression (possibly associated with hypercortisolemia) may persist for years after the resolution of the depression and the presumed hypercortisolemic state (Sheline et al. 1999); however, see Shah et al. (1998), although the direction of any causality in such studies remains questionable, as does the

Figure 2
A simplified, theoretical model of the relationship between stress, antidepressants, corticosteroid activity, neurotransmitter activity, neurotrophin expression and hippocampal cell viability. Potential sites of intervention are keyed to the bracketed numbers in the figure. References to the specific pathways and potential sites of intervention are provided in the text.
linkage with hypercortisolemia. Interestingly, even in the absence of gross morphological damage (e.g., major loss of pyramidal cell neurons), rare but convincing signs of apoptosis are seen in hippocampal tissue from patients with major depression and from medically ill patients treated with glucocorticoid medication (Lucassen et al 2001).

The question of reversibility of glucocorticoid-induced hippocampal damage is immensely important, both clinically and theoretically, and the best data addressing this question derive from animal studies. Recent data in rats suggest reversibility of neuronal damage ('structural reorganization') following recovery from chronic stress or glucocorticoid administration, possibly due to neurogenesis (Souza et al 2000). However, tree shrews exposed to chronic stress or month-long cortisol administration showed residual 'traces' of impairment even after seven weeks of recovery (Ohl et al 2000). Tree shrews in both the stressed and cortisol treatment groups, studied longitudinally in a within subject design, showed a tendency towards a reduction in MRI-determined hippocampal volume (of about 5-10%, p< 0.16); this failed to normalize after the seven weeks of recovery. Hippocampus-mediated memory in the cortisol-treated group was impaired during cortisol treatment but showed recovery by seven weeks post-treatment. The chronically stressed group, however, showed memory impairments that developed only after termination of the stress (Ohl et al 2000).

• Peripheral effects: metabolic syndrome

As in the brain, cortisol affects cellular targets possessing cortisol receptors throughout the periphery. Chronic exposure to elevated levels of cortisol without the protective effects of anabolic hormones, such as DHEA, can have extensive effects on physiological functioning, and, in particular, on aspects of metabolism (as can be seen in chronic stress, depression and Cushing's syndrome) (McEwen 1998; McEwen and Stellar 1993; Seeman et al 1997). These effects on physiology may be important contributing factors to the high comorbidity of Metabolic Syndrome X and other chronic diseases with depression (Björntorp 2001).

Cortisol is intimately involved in regulating caloric consumption, insulin sensitivity and fat deposition. Chronically elevated, unopposed glucocorticoid activity is thus associated with indicators of metabolic dysregulation such as increased eating behaviour (Epel et al 2001b), changes in body composition such as increased visceral (central) adiposity and fat-to-lean mass ratio, peripheral muscle wasting, and insulin resistance (Björntorp 2001). Below we examine evidence that cortisol may influence risk for disease through inducing Metabolic Syndrome X features.

Appetite and food consumption
Eating behaviour is an important link between depression, stress and certain chronic diseases. Both negative mood (Greeno and Wing 1994) and cortisol may stimulate appetite and eating (Sapolsky et al 2000). Glucocorticoids lead to hyperphagia and weight gain in rodents prone to obesity (Bray 1985). Relationships between cortisol and eating behaviour have been studied less frequently in humans, but several studies suggest that elevated cortisol stimulates appetite and food consumption. High cortisol reactivity in response to a laboratory stressor predicted greater caloric consumption, especially of sweet food, in the stress recovery period in healthy women (Epel et al 2000b). Further, exogenously administered glucocorticoids significantly increase appetite and food intake (Tataranni et al 1996). Eating in turn, especially high fat food, stimulates the HPA axis (Tannenbaum et al 1997), possibly creating a positive feedback loop of subsequent eating behaviour and increased cortisol. Thus, elevated basal or reactive cortisol may be implicated in overeating and obesity, and possibly in obesity-related metabolic diseases.

Visceral fat
Central or visceral obesity (as opposed to generalized obesity) is an important risk factor for chronic disease (Kissebah and Krakower 1994). Depressions or stress and stress-eating behaviour may work synergistically to promote fat deposition, especially visceral fat. Raikkonen et al found that anger and depression ratings predicted increased visceral fat (Raikkonen et al 1999), as well as a cluster of factors related to the metabolic syndrome (Raikkonen et al 2001). Many years later in post-menopausal women. Primate and rodent studies have also shown that exposure to chronic stress increases visceral fat preferentially over peripheral fat (Jayo et al 1993; Rebuffe-Scrive et al 1992). Hypercortisolemia, or limbic-hypothalamic-pituitary-adrenal (LHPA) axis dysregulation, is a likely mediator of these effects. In humans, visceral fat deposition is associated with Cushing's syndrome, hypercortisolemia major depression (Thakore et al 1997) and HPA axis dysregulation in a non-clinical sample (Pasquali et al 1996). High reactivity to stress, even amidst normal basal cortisol levels, is similarly associated with increased visceral fat. In a non-clinical healthy sample, women with greater visceral fat had basal cortisol levels comparable to women with predominant peripheral fat but had greater life stress and exaggerated cortisol reactivity to psychological stress (Epel et al 2000a). Together, these studies provide another example of associations between stress-induced cortisol and a major indicator of metabolic dysregulation, with suggestion of a causal effect of glucocorticoids, based on animal studies.

Insulin resistance and diabetes
In rats, exposure to chronic stress increases hy-
perglycemia, insulin resistance and blood lipids (Surwit and Williams 1996). Elevated levels of glucocorticoids can also decrease insulin sensitivity (Bjorntorp 1997; Rizza et al 1982; Sapolsky et al 2000). Despite a wealth of circumstantial evidence (Bjorntorp 1997), no controlled studies have demonstrated that a chronically stressed or depressed human sample also has actual insulin resistance (using the gold standard clamp method, rather than proxy measures such as fasting insulin levels), and whether this is mediated by LHPA axis hyperactivity. On the other hand, Bjorntorp and colleagues have found that LHPA axis dysregulation, in the form of a blunted cortisol rhythm and sluggish response to stimuli, rather than cortisol hyperactivity, is related to components of the metabolic syndrome (Bjorntorp et al 1999b). However, it is unclear whether this particular profile of LHPA axis dysregulation precedes or follows the other signs of metabolic dysregulation.

Type II diabetes may develop from insulin resistance, and is highly comorbid with major depression (Geringer 1990). A prospective study found that depression ratings in a community population predicted onset of diabetes mellitus eight years later (Kawakami et al 1999). There are likely bi-directional relations between depression and diabetes, and a possible common underlying diathesis is LHPA axis dysregulation. In fact, even in nondepressed diabetics, there is higher DST non-suppression (43% non-suppressors) compared to normal controls (Hudson et al 1984).

Patients with adrenal adenomas provide a clear example of the somatic effects of chronic exposure to excessively high endogenously produced cortisol levels and of the comorbidity between depression and allostatic load or frank disease. Cushing’s syndrome leads to central obesity, muscle wasting, high blood pressure, insulin resistance and osteoporosis (Newell-Price et al 1999). In patients without frank Cushing’s syndrome, adrenal masses (“incidentalomas”) are a relatively common type of tumour and are typically thought to be asymptomatic, though a recent clinical evaluation showed otherwise. Rossi and colleagues found that subtle hypercortisolemia due to such masses is frequent in a normal population, and health sequelae may be as well (Rossi et al 2000). In studies examining symptoms of such adrenal masses, participants who met criteria for subtle hypercortisolemia showed signs of hypertension, impaired glucose tolerance or diabetes, hyperlipidemia and obesity (Rossi et al 2000; Reincke 2000). Compared to a control group, they had a lower anabolic balance and greater LHPA axis dysregulation (higher cortisol, lower ACTH, less cortisol suppression to dexamethasone, and lower DHEA-S and DHEA-S responsivity to ACTH). Surgical removal of adrenal masses led to remission of these symptoms.

As in the CNS, DHEA has antiglucocorticoid effects in the periphery. In animals, DHEA may antagonize some of the peripheral catabolic effects of glucocorticoids by increasing sensitivity to insulin, enhancing adipocyte glucose uptake and diminishing hyperglycemia (Coleman et al 1982) and reducing adiposity (Dong-Ho et al 1998), but similar effects have not been uniformly found in humans (Wellman et al 1999). However, in humans, other anabolic hormones such as testosterone in men and IGF-1 and growth hormone in both genders, especially for those who are growth hormone deficient, can reverse metabolic defects such as visceral and total adiposity (Marin 1995; Thompson et al 1998) and decrease insulin resistance (Berneis and Keller 1996) and, in many cases, depressive symptoms (Thompson et al 1998).

Exogenous corticosteroid effects

- **Steroid psychosis**
  Several clinical models highlight the ability of glucocorticoids to regulate human behaviour, and each poses important theoretical and treatment issues. Among the earliest indications was the observation of behavioural changes, occasionally profound (e.g., delirium, confusion, insomnia, emotional lability, depression, hypomania, attentional impairments, sensory flooding, psychosis and even suicidality) in medically ill patients prescribed cortisone, dexamethasone, prednisone and other synthetic glucocorticoids (Hall et al 1979; Ling et al 1981; Naber et al 1996; Pies 1995; Wolkowitz et al 1997a; Wolkowitz et al 1990b; Reus and Wolkowitz 1993; Boston Collaborative Drug Surveillance Program 1972).
  Such severe reactions, occurring even in patients with no prior psychiatric history, are frequently termed "steroid psychosis." Whereas synthetic glucocorticoid medication-induced affective changes are often activation and manic-like initially, they typically become more depressive in nature with continued steroid treatment (Plihal et al 1996). Recent studies have also highlighted the deleterious effects of glucocorticoid medication on memory in both patients and normal controls (Keenan et al 1996; Keenan et al 1995; Kirschbaum et al 1996; Lupien and McEwen 1997; Newcomer et al 1999; Varnay et al 1984; Wolkowitz et al 1997a; Wolkowitz et al 1990a; Wolkowitz et al 1993c).
  In light of the preceding discussion of the primary anatomic loci of glucocorticoid effects in the brain, it is notable that these studies have generally reported specific disruption of hippocampus- (and, in some cases, frontal cortex-) mediated memory functions (such as disruption of explicit, episodic and declarative memory, with sparing of non-hippocampus-mediated implicit, procedural and semantic memory). A number of biochemical and brain electrophysiological correlates of exogenous glucocorticoid-induced behavioural and cognitive changes have been elucidated (Wolkowitz et al 1996).

Although infrequently described in the literature, a small percentage of glucocorticoid-treated patients (perhaps up to 7%) may experience a "steroid dementia syndrome," or long-lasting memory impairment (again, hippocampal in nature) even after cessation of glucocorticoid medication (Lewis and Smith 1983; Reckart and Eisendrath 1990; Varney et al 1984; Wolkowitz et al 1997a). As noted earlier, a small proportion of steroid-treated patients shows signs of hippocampal neuronal apoptosis, as well as heat shock protein 70 staining (an index of response to oxidative damage and cellular stress), at autopsy (Lucassen et al 2001).

• Treatment

Surprisingly, few studies have addressed treatment options for patients suffering from steroid psychosis or for patients withdrawn from steroids who have persisting "steroid dementia." Anecdotally, lithium, antipsychotic drugs and anticonvulsants have been used with varying degrees of effect, either prophylactically or in treating acute symptoms (reviewed in: Reus and Wolkowitz 1993; Wolkowitz et al 1997a). Several novel experimental approaches have also been suggested for the treatment or prophylaxis of steroid psychosis. McEwen and Magarinos (McEwen and Magarinos 2001), examining the role increases in serotonin and excitatory amino acid levels may play in steroid-associated hippocampal damage, suggest that tianeptine (a serotonin reuptake enhancer) and phenyltoin (which blocks excitatory amino acid release and actions) may lessen such deleterious effects. Also, based on the suggestion that steroids potentiate metabolic insults to the hippocampus via impaired neuronal glucose uptake (reviewed above), Sapolsky (Sapolsky 1994) suggests that glucose or mannose co-administration might be protective, as might decreasing neuronal stimulation and energy demands. Lastly, co-administration of dehydroepiandrosterone (DHEA), along with the prescribed glucocorticoid medication, might allow the usage of lower glucocorticoid doses in some situations and might buffer certain deleterious neuropsychiatric and somatic effects of the glucocorticoid (Koo et al 1987; Straub et al 2000; Van Vollenhoven et al 1994; Dubrovsky 1997). DHEA co-administration makes particularly good sense from the vantage point of maintaining an optimal "anabolic balance," since prolonged glucocorticoid treatment inhibits ACTH secretion, involutes the adrenal cortex and results in diminished endogenous DHEA secretion (Robinson and Cutolo 1999). This strategy, however, remains inadequately tested except in the treatment of systemic lupus erythematosus (van Vollenhoven 1997; Van Vollenhoven et al 1994). Interestingly, some of the catabolic effects of long-term prednisone treatment have proven reversible by administration of other anabolic hormones, GH or IGF-1 (Moxley 1994).

While studies with exogenous glucocorticoids clearly demonstrate the potential of such hormones to induce psychiatric symptoms, it is not possible to extrapolate directly from their effects to those of endogenous hypercortisolemia (Pilial et al 1996; Wolkowitz 1994; Wolkowitz et al 1997a). Endogenous states of glucocorticoid excess are discussed in the following sections.

Endogenous glucocorticoid effects

Neuropsychiatric syndromes

Cushing's Syndrome

Cushing's syndrome is associated with a very high incidence of fatigue, decreased energy, irritability, decreased memory and concentration, depressed or labile mood, anxiety, decreased libido, insomnia and crying (Starkman et al 1981; Trethowan and Cobb 1952; Whelan et al 1980). These symptoms are reminiscent of those commonly seen in major depression (Haskett 1985), although certain differences, such as a preponderance of "atypical" depressive features in Cushing's syndrome patients, may exist (Kling et al 1991; Loosen et al 1992). Neuropsychiatric symptoms in Cushing's syndrome patients are directly correlated with circulating cortisol levels (Cohen 1980; Starkman et al 1981). As was the case with individuals administered exogenous glucocorticoids, patients with Cushing's syndrome demonstrate a pattern of cognitive disturbance that is consistent with hippocampal dysfunction (involving episodic but not semantic memory) (Martignoni et al 1992; Mauri et al 1993). Cushing's syndrome patients also have diminished hippocampal formation volume (assessed radiographically) (Starkman et al 1992) that has been directly correlated with cognitive performance and inversely correlated with urinary free cortisol output (Starkman et al 1992).

Antiglucocorticoid treatment

al 1991; Verhelst et al 1991; Voigt et al 1985; Welbourn et al 1971; Zeiger et al 1993; Berwaerts et al 1998; Saad et al 1984; Hirsch et al 2000), in direct proportion to the reductions in circulating cortisol levels. At least 31 separate reports have documented decreased depression, anxiety, suicidality, irritability, psychosis and cognitive impairment, and even complete psychiatric remission, in Cushings patients who received either surgical or medical (e.g., ketoconazole, metyrapone, aminoglutethimide, RU-486) treatment aimed at lowering cortisol levels or cortisol activity. The largest two case series documented a response rate of 70-73% of treated patients (Sonino et al 1993; Verhelst et al 1991), although, in several cases, psychiatric improvement was erratic, delayed or incomplete (Haskett 1985; Hammers 1955; Ernest and Ekman 1972). In rare cases, psychiatric status apparently fails to recover despite adequate treatment, possibly in association with cerebral cortical atrophy (Mancini et al 1999). Most of these antiguocorticoid treatment trials have been reviewed in greater detail elsewhere (Wolkowitz and Reus 1999).

Levels of steroid hormones other than cortisol, which are also abnormal in Cushings syndrome patients and which also have neuroactive properties, such as DHEA, have received virtually no attention to date (Dubrovsy 1991; Levine and Mitty 1988; Murphy 1991a). Indeed, the anabolic balance, e.g., the ratio of DHEA to cortisol, may be more important than cortisol alone in determining severity of depression and cognitive impairment in these patients (Dubrovsy 1991; Dubrovsy 1997). Further difficulty in interpreting the Cushings syndrome literature is that patients with Addisons disease (adrenocortical insufficiency) also frequently present with depression and cognitive impairment (Cleghorn 1951; Leigh and Kramer 1984); in such patients, psychiatric disturbances are negatively correlated with serum cortisol levels (Lobo et al 1988), and glucocorticoid (Riedel et al 1993) and DHEA (Arti et al 1999; Arti et al 1998) administration both relieve the psychiatric symptoms. The relationship between cortisol and neuropsychiatric function is undoubtedly complex and may even resemble an inverted U-shaped dose-response curve, with optimal functioning at mid-range levels (Lupien and McEwen 1997; McEwen 1987).

In general, antiguocorticoid strategies (as well as pituitary or adrenal surgery) are also effective at reversing the physical complications of Cushings syndrome. In fact, they may be more effective than traditional treatment targeted to individual somatic symptoms (Neto et al 2000). Antiguocorticoid medication normalizes blood pressure, blood sugar control, hypokalemia, hirsutism and menstrual disturbances in the majority of Cushings syndrome patients (Sonino et al 1991).

• Major depression and other conditions

Neuropsychiatric syndromes

Hypercortisolemia and resistance of the LH/HPA axis to suppression by dexamethasone ("DST nonsuppression") are the most widely replicated biological abnormalities in major depression, affecting up to one half of depressed patients. The degree of cortisol hypersecretion is directly correlated with the extent of certain behavioral alterations such as sleep disturbance, decreased energy, decreased attention and cognitive performance, psychosis, psychomotor disturbance and anxiety (Reus 1982; Wolkowitz and Reus 1999; Wolkowitz et al 1994).

As was the case with Cushings syndrome patients, depressed patients may have hippocampal volume loss (Shah et al 1998; Sheline et al 1999) along with deficits in hippocampal-mediated cognitive function (Shah et al 1998; Sheline et al 1999; Wolkowitz et al 1999). In one report, this hippocampal volume abnormality persisted for years after clinical recovery from depression and was directly correlated with the number of lifetime days of depression (Sheline et al 1999), which may itself be a marker of lifetime exposure to stress levels of cortisol, although this remains to be further tested. In the other study, however, hippocampal volume loss, which was seen in chronically depressed patients, was not seen in previously depressed patients who had been recovered for an average of three months (Shah et al 1998).

Persistent cortisol hyperactivity (manifest as DST nonsuppression, high cortisol response to the combined dexamethasone-CRH test or elevated evening cortisol-to-DHEA ratios) following apparent clinical recovery is strongly associated with early relapse and poor outcome on follow-up (Goodyer et al 1998; Greder et al 1983; Ribeiro et al 1993; Zobel et al 1999), suggesting that LH/HPA axis normalization is a prerequisite for more abiding recovery. Traditional antidepressant medications increase brain levels of corticosteroid receptors, rendering individuals more sensitive to glucocorticoid negative feedback. A recent body of literature, reviewed by Holsboer and Barden (Holsboer and Barden 1996), suggests that these effects are shared by most antidepressants, and that the time course of these changes parallels that of clinical antidepressant responses. These authors hypothesized that a primary and common mechanism of action of antidepressants is the stimulation of corticosteroid receptor expression, leading to enhanced negative feedback, lowered LH/HPA activity and lowered levels of CRH and cortisol. Secondary effects of lowered cortisol levels would be a lessening of expression of genes that are under glucocorticoid regulatory control (e.g., those related to biogenic amine neurotransmission, as reviewed above), and secondary effects of lowered CRH levels would be a lessening of
anxiety and certain depressive symptoms (as reviewed below). This re-conceptualization of antidepressant action is directly relevant to the primary thesis of this review, and it accords with the treatment data reviewed below.

**Substance abuse**

Another rapidly evolving area of study is the possible role of LHPA axis dysregulation in the relationship between stress and substance abuse. In fact, the high comorbidity between depression and substance abuse and dependence may depend in part on common alterations in glucocorticoid regulation. A variety of animal and human studies have documented that glucocorticoids alter the acute psychomotor and reinforcing effects of psychostimulant and sedative-hypnotic drugs, and modulate the phenomenon of stress-induced relapse (Deroche et al 1997; Goeders and Le Moal 1996; Sinha et al 1999; Sinha et al 2000; Stewart 2000). Whether strategies directed at blocking the LHPA response to reinforcing drugs (such as the strategies outlined in the following section) will lead to a decrease in substance self-administration and, ultimately, to a practical therapeutic intervention, is presently unknown.

**Antiglucocorticoid treatment**

It is surprising that, until 1991, few studies had assessed the behavioural effects of direct pharmacological lowering of cortisol levels in patients with major depression. At present, there are 12 studies of antiglucocorticoids (as solitary treatments) in treating depression; only four of these were single- or double-blinded. These studies are reviewed in greater detail elsewhere (Wolkowitz and Reus 1999). In interpreting these studies, it is important to consider that, although cortisol was the major endocrinological "target" of the endocrinological interventions, the synthesis of other steroid hormones was invariably affected by these drugs (Figure 3). Figure 3 displays the sites of enzymatic blockade of several steroid biosynthesis inhibitors. As is evident, enzymatic blockade with these agents affects the synthesis of multiple steroid hormones, rendering the actual mechanism of any observed behavioural effects indeterminate.

In each of the studies utilizing the antiglucocorticoid approach (Amsterdam et al 1994; Anand et al 1995; Ghadirian et al 1993; Heinz and Piazza et al 1996; Sinha et al 1999; Sinha et al 2000; Stewart 2000), whether strategies directed at blocking the LHPA response to reinforcing drugs (such as the strategies outlined in the following section) will lead to a decrease in substance self-administration and, ultimately, to a practical therapeutic intervention, is presently unknown.

![Figure 3](image)

**Figure 3**

Steroid metabolic pathway and sites of antiglucocorticoid enzymatic blockade.

SCC = side chain cleavage; OH = hydroxylase; HSD = hydroxysteroid dehydrogenase; SST = steroid sulfotransferase. 1 = site of blockade by ketoconazole; 2 = site of blockade by metyrapone; 3 = site of blockade by aminoglutethimide; 4 = site of blockade by...
least a partial antidepressant response, and 46.2% showed a "full" or clinically meaningful response. These results must be interpreted very cautiously due to the small sample sizes in all of these studies.

Endocrinological predictors and correlates of antiglucocorticoid response remain uncertain. While it is appealing to postulate that patients who are hypercortisolemic (or DST non-suppressing) at baseline are most likely to respond to this approach, few studies have meaningfully assessed this. In an early study by Murphy et al (Murphy 1991a), five of six antiglucocorticoid treatment responders who were DST non-suppressors before starting therapy had reverted to normal suppression when tested after completion of therapy; the one patient who did not revert to normal suppression suffered an early relapse (Murphy and Wolkowitz 1993). Baseline 8:00 a.m. serum cortisol levels, however, did not predict treatment response, and treatment-associated decreases in 8:00 a.m. serum cortisol levels were inconsistent and not statistically significant. Other studies, however, have noted significant correlations between antiglucocorticoid-associated antidepressant effects and changes in cortisol levels. Anand et al (Anand et al 1995), for example, in a double-blind case report utilizing ketoconazole, noted clinically significant improvements in depression and memory in one treatment-resistant patient; treatment-associated decreases in cortisol levels were closely related to decreases in depression ratings. Wolkowitz et al (Wolkowitz et al 1993b) also reported that ketoconazole, administered to medication-free depressed patients in an open-label manner for three to six weeks, significantly improved depression ratings and significantly decreased 4:00 p.m. serum cortisol levels. Changes in Beck Depression Inventory ratings were directly correlated with changes in serum cortisol levels. These researchers subsequently reported on a sample of depressed patients treated with ketoconazole in a double-blind, placebo-controlled trial (Wolkowitz et al 1999a). Of 20 patients studied, eight were hypercortisolemic at baseline (4:00 pm serum cortisol >10 mg/dl) and 12 were eucortisolemic. Whereas no significant main effect of ketoconazole vs. placebo on depression ratings was observed, there was a significant interaction of drug (ketoconazole vs. placebo) x baseline cortisol status (eucortisolemic vs. hypercortisolemic). Specifically, ketoconazole was superior to placebo in alleviating depressive symptoms in the hypercortisolemic but not in the eucortisolemic patients. These findings are consistent with the hypothesized specificity of antiglucocorticoid benefits in hypercortisolemic states and raise the possibility of biologically distinct sub-groups of patients with major depression. Such conclusions must remain tentative, however, due to the very small sample size of this and other studies.

Two other studies have attempted to clarify the mechanisms by which antiglucocorticoids might alleviate depression. Thakore and Dinan (Thakore and Dinan 1995) treated eight depressed patients with ketoconazole for four weeks and noted significant antidepressant effects (average decrease in depression ratings = 60%) and significant decreases in serum cortisol levels. They had postulated that elevated cortisol activity might provoke or maintain depressive symptoms via the induction of serotonin system sub-sensitivity (as reviewed above). They based their hypothesis partially on observations that, in depressed patients, baseline cortisol levels are inversely related to the magnitude of serum prolactin (PRL) responses to 5HT agonists such as d-fenfluramine (a putative marker of serotonin system sensitivity). To test this hypothesis, they administered the d-fenfluramine challenge to their subjects at baseline and after four weeks of ketoconazole treatment. Ketoconazole normalized the PRL response to d-fenfluramine (i.e., increased the response relative to baseline), and the increases in PRL responses were significantly correlated with reductions in depression ratings. These findings are consistent with the notion that hypercortisolemia down-regulates 5HT system sensitivity (as suggested by the animal studies reviewed above), and that antiglucocorticoid treatments may have antidepressant effects via a normalization (increase) of 5HT sensitivity.

Lastly, O'Dwyer et al (O'Dwyer et al 1995) treated eight depressed patients with metyrapone (plus replacement doses of hydrocortisone) vs. placebo in a single-blind manner in a two-week-per-arm crossover design and noted significant decreases in depression ratings as well as in serum cortisol levels during metyrapone treatment. After discontinuation of metyrapone, depression ratings remained low despite return of cortisol to baseline levels. Checkley et al (Checkley et al 1994), commenting on the same group of subjects as O'Dwyer et al (O'Dwyer et al 1995), noted that, in addition to normalizing cortisol levels, metyrapone led to an increased urinary excretion of the neuroactive steroids, tetrahydro-11-deoxy cortisol and tetrahydrodeoxy corticosterone (THDOC). They suggested that either the decreases in cortisol levels or the increases in levels of these "neurosteroids" may have been related to the antidepressant effects (Checkley et al 1994; Raven et al 1995). The latter possibility is important to entertain when evaluating the literature on antiglucocorticoids in depression, since several of the treatment studies reviewed above failed to demonstrate decreases in serum cortisol levels despite demonstrating significant antidepressant effects, and since neurosteroid hormones, such as pregnenolone, DHEA and allopregnanolone, that are altered by stress and depression, are also affected by antidepressant and antiglucocorticoid drugs (Murphy 1991b; Griffin and Mellon 1999;
In addition to studies of antiglucocorticoids used alone in depression, other studies have examined their utility in treating other psychiatric conditions or as augmentation agents in patients with treatment-resistant depression and other psychiatric illnesses. For example, refractory anxiety disorders associated with late-onset congenital adrenal hyperplasia benefited from adrenal suppressive doses of ketoconazole (Jacobs et al 1999). Beneficial effects of antiglucocorticoid adjunctive treatment have been noted in some patients with refractory bipolar I and II depression (Brown et al 2001; Ravaris et al 1994), in severe refractory obsessive compulsive disorder patients (Chouinard et al 1996), in depressed schizophrenic and schizoaffective disorder patients (Marco et al In Review), and in a patient with treatment-resistant depression and a coexisting "metabolic syndrome" comprised of hypercortisolemia, hypertension and insulin resistance (Bech et al 1999). The latter example represents the importance of treating the presumed neuroendocrine causes of comorbidity.

### Alternate antiglucocorticoid and glucocorticoid treatments in depression

- **Steroid receptor antagonist: RU-486**
  RU-486 (Mifepristone) does not inhibit steroid biosynthesis but blocks progesterone and, at higher doses, glucocorticoid (Type II) receptors in the brain. Indeed, circulating cortisol levels may significantly increase secondary to RU-486's receptor blockade. In preclinical models, RU-486 has been found to significantly protect hippocampal neurons from oxidative stress-induced damage (Behl et al 1997). Early trials treating depressed patients with RU-486 in Canada showed promising results, but studies were curtailed due to unavailability of the drug at that time (Murphy et al 1993). Ongoing studies at Stanford University, using four days of RU-486 treatment vs. placebo in the treatment of psychotic depression, have reportedly found some signs of efficacy in the small number of patients treated to-date, although psychotic and cognitive symptoms seemed to respond better than depressive ones (Belanoff and Schatzberg 2000). The use of RU-486 for other than subacute administration has been infrequently studied and has been associated with occasional rashes (Murphy et al 1993). Other corticosteroid receptor blocking compounds, such as ORG-34116, are in development (Karst et al 1997).

- **Dexamethasone, prednisone and hydrocortisone**
  In what seems a diametrically opposite approach to altering steroidal activity in depressed patients, Arana and colleagues (Arana 1991; Arana et al 1995; Beale and Arana 1995) reported antidepressant effects of acute high dose dexamethasone administration. In this paradigm, dexamethasone was administered intravenously as a one-time bolus of 4-8 mg or orally as 4 mg per day for four days. Results of the open-label intravenous dexamethasone trial indicated an average 56% improvement within 10 days in 75% of depressed subjects, including five of seven treatment-refractory ones who had failed at least two prior antidepressant trials. In the blinded oral dexamethasone trial, dexamethasone was associated with only a 27.5% improvement in depression ratings compared with a 13.6% improvement with placebo. A significantly greater number of dexamethasone-treated subjects responded to treatment than placebo-treated subjects. The authors suggested that the beneficial effect of dexamethasone was secondary to regulation of CRH receptors, increased serotonergic activity or other geno-

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- **Corticotropic releasing hormone (CRH) receptor antagonists**
  Elevated CSF CRH levels have been frequently described in depressed patients compared to controls (Nemeroff 1988; Nemeroff 2000), although
mically mediated changes in neurotransmission. Alternative explanations are offered below.

Similar results were obtained by another group using an open-label design. Dinan et al (Dinan et al 1997) studied 10 depressed patients who had not responded to sertraline or fluoxetine, and added dexamethasone, 3 mg p.o. daily for four days, to the ongoing antidepressant regimen. By the following day (Day 5), three of the six sertraline patients and three of the four fluoxetine patients demonstrated significant antidepressant responses (50% reduction in depression ratings). Remarkably, this initial improvement was maintained through Day 21, the last assessed day. Cortisol changes in response to dexamethasone treatment were not reported, but baseline morning serum cortisol levels were directly correlated with antidepressant responses (viz., higher baseline cortisol was associated with better responses to dexamethasone). The dexamethasone was relatively well tolerated, but several patients reported sleep disruption, nausea and/or anxiety during dexamethasone treatment. More recently, Bodani et al (Bodani et al 1999) described two elderly patients with resistant depression who appeared to benefit from dexamethasone treatment, and Hardy et al (Hardy et al 2001) noted that terminally ill cancer patients generally experienced mood improvement with sub-chronic dexamethasone treatment.

Finally, Wolkowitz et al (Wolkowitz et al 1996) reported negative results in a very small, double-blind replication study. Five depressed patients received one-time intravenous infusions of either 6 mg dexamethasone or placebo and were evaluated 10 days later. The three subjects who received dexamethasone all fared more poorly than the two who received placebo; two of the three dexamethasone-treated subjects actually worsened following treatment, and the trial was discontinued. The one dexamethasone-treated subject who showed any antidepressant effect had the lowest baseline serum cortisol concentration of the group. This observation is perhaps consistent with a case series of hypocortisolemic atypical depressed patients who responded favourably to antidepressant augmentation with prednisone (Bouwer et al 2000). The authors of the latter report theorized that either hyper- or hypocortisolism may be associated with depressive symptoms (perhaps related to "typical" vs. "atypical" symptom profiles, respectively), and that the hypocortisolemic subgroup might respond preferentially to glucocorticoid augmentation therapy (Ibid.).

In a related strategy, several investigators have assessed the mood-altering effects of cortisol (hydrocortisone) (Cameron et al 1985). In one small-scale study, Goodwin et al (Goodwin et al 1992) noted that an acute cortisol infusion transiently improved self-rated mood in 12 depressed patients. These patients were not hypercortisolemic at baseline, and long-term antidepressant effects were not assessed. DeBattista et al (DeBattista et al 2000) acutely treated, in a double-blind manner, six depressed patients with hydrocortisone (15 mg i.v. over 2 hours), six patients with ovine CRH (1 mcg/kg i.v.) and 10 patients with placebo at 7:00 p.m. and assessed depression ratings the following day at 4:00 p.m. Hydrocortisone-treated patients, compared to both placebo and CRH-treated ones, showed a significant acute antidepressant response. It was not reported whether the antidepressant responses were related to baseline cortisol levels, whether they were correlated with increases in circulating cortisol levels, or whether the antidepressant responses persisted beyond one day.

If acute dexamethasone treatment proves to have antidepressant effects, how might this be reconciled with antiglucocorticoids having similar effects? Antiglucocorticoids and dexamethasone administration could both have antidepressant effects via: (1) their common effect of curtailing endogenous cortisol synthesis; (2) inducing up-regulation of brain glucocorticoid receptors (with the effect of re-establishing effective negative feedback) (Pepin et al 1996); (3) altering levels of other adrenal or neurosteroid hormones (e.g., shifting cholesterol metabolism in the direction of increased synthesis of certain GABAergic neurosteroids) (Raven et al 1996; Romeo et al 1998); or (4) increasing ACTH levels (with acute high dose dexamethasone treatment, this might occur after dexamethasone's acute inhibitory effects are terminated and the suppressed LHPA axis signals increased ACTH output). Additionally, recent evidence suggests that dexamethasone is actively excluded from brain and does not replace endogenous glucocorticoids at hippocampal MR and GR sites (De Kloet et al 1998). Its behavioural effects, therefore, may result from indirect effects of dexamethasone-induced ACTH and cortisol suppression on the balance of occupation of the two corticosteroid receptor types in the hippocampus (De Kloet et al 1998). Antiglucocorticoids and dexamethasone, then, could share the net effect of increasing hippocampal MR relative to GR occupation: antiglucocorticoids by directly lowering cortisol levels to a degree insufficient to occupy brain GR, and dexamethasone by binding to pituitary, but not hippocampal, GR, resulting in decreased cortisol levels and lessened brain GR occupation (Plihal et al 1996). Plihal et al, have suggested that MR activation, as opposed to GR activation, induces positive mood states (Plihal et al 1996). The beneficial effects of hydrocortisone, if confirmed, are more difficult to explain, unless the effects are transient (Plihal et al 1996) and secondary, perhaps, to increased dopamine levels (DeBattista et al 2000; Wolkowitz et al 1986). Alternatively, even in the face of persistent
hypercortisolemia, phasic ("burst") increases in cortisol levels may induce a rapid "re-setting" of LHPA axis negative feedback control (DeBattista et al 2000; Murphy 1991a). Lastly, as suggested above, it is possible that different subgroups of depressed patients respond differentially to corticosteroid augmentation vs. suppression, perhaps related to their baseline adrenocortical output (Bouwer et al 2000; DeBattista et al 2000; Wolkowitz et al 1996). Considerably more work needs to be done to determine the predictors and mediators of glucocorticoid-based treatments of depression as well as their long-term effects.

**• Dehydroepiandrosterone (DHEA) and neurosteroids**

We have discussed previously that DHEA may serve as one of the body's endogenous "anti-cortisol" hormones and that the ratio of DHEA-to-cortisol (the "anabolic balance") may be more informative regarding psychiatric and health status than levels of either hormone alone (Ferrari et al 2001; Hechter et al 1997; Leblhuber et al 1992; Wolkowitz et al 1992). Indeed, multiple studies have verified DHEA's ability, both in vitro and in vivo, to antagonize certain of cortisol's physiological effects (Browne et al 1992; Hechter et al 1997; Kalimi et al 1994; Patchev and Almeida 1997; Svec and Porter 1998) and to prevent certain physiological sequelae of stress (Hu et al 2000; Singh et al 1994). In particular, DHEA administration can reverse important detrimental effects of glucocorticoids in the CNS (Dubrovsky 1997; Kimonides et al 1999), can have neuroprotective and cognition-enhancing effects and can counteract the development of "depression-like" behaviours in animals [reviewed in (Kroboth et al 1999; Svec and Porter 1998; Wolkowitz et al 2000a)]. Conversely, high levels of glucocorticoids or exposure to high levels of stress can block DHEA's beneficial neurosteroid actions (Diamond and Fleschner 2000).

Whereas multiple beneficial effects of DHEA have been observed in rodent models, rats and mice produce little adrenally-derived DHEA naturally, so these findings may be of limited generalizability to humans. Nonetheless, several studies reviewed in detail elsewhere raise the possibility that decreased DHEA(S) levels (or decreased DHEA(S)-to-cortisol ratios) contribute to the development or progression of affective disturbances, cognitive decline, fatigue and impaired physical and emotional well-being in humans (Wolkowitz et al 2000a; Kroboth et al 1999; Svec and Porter 1998; Seeman et al 2001), although it is possible that differing patterns are seen in men vs. women (Kroboth et al 1999).

Regardless of whether low endogenous levels of DHEA are associated with depression, cognitive impairment or physical disease risk factors in humans, exogenous supplementation with DHEA may have therapeutic effects and counteract certain deleterious effects of allostatic load. DHEA treatment reportedly has antidepressant effects in patients with major depression (Wolkowitz et al 1995; Wolkowitz et al 1999b; Wolkowitz et al 1997b) and dysthymia (Bloch et al 1999), mildly and transiently improves cognitive performance in patients with Alzheimer's disease (Wolkowitz et al 2000b) and enhances well-being, energy and libido in hypo-adrenal patients with Addison's disease (Artl et al 1999; Artl et al 1998; Hunt et al 2000). However, as is the case with most antidepressants, DHEA treatment can result in overactivation, mania or psychosis in some patients (Howard III 1992; Kline and Jaggers 1999; Markowitz et al 1999).

Beneficial mood and memory effects of DHEA treatment in normal individuals and in very mildly symptomatic populations have been demonstrated less consistently (Barnhart et al 1999; Diamond et al 1996; Hurpbert and Van Niekerk 2001; Morales et al 1994; Wolf et al 1997). Improvements in anthropometric indices of allostatic load, such as muscle-to-fat ratio, fasting glucose and insulin levels and bone mineral density, have been noted in healthy volunteers in some, but not all studies (Baulieu et al 2000; Diamond et al 1996; Labrie et al 1997; Morales et al 1998; Nestler et al 1988), although again, gender differences may have been apparent (Baulieu et al 2000; Morales et al 1998). Despite the widespread use of DHEA in the United States, more studies are needed before any conclusions are reached regarding any beneficial effects (Katz and Morales 1998; van Vollenhoven 1997; Wolkowitz et al 2000a; Wolkowitz and Reus 2000; Kroboth et al 1999).

To the extent DHEA treatment improves mood and sense of well-being by improving "anabolic balance" (as discussed in the introduction to this article), other anabolic hormones might have similar effects. Indeed, recent epidemiological and cross-sectional studies have demonstrated positive correlations between serum levels of bioavailable testosterone and ratings of mood and cognitive function in men (Barrett-Connor et al 1999; Morley et al 1997). Testosterone replacement therapy does improve mood in hypogonadal and elderly men and men with HIV disease (Wang et al 1996; Seidman and Walsh 1999; Rabin et al 2000), but effects in eugonadal patients with major depression are less clear (Margolese 2000; Seidman and Walsh 1999). Growth hormone treatment typically has positive effects on mood and cognitive function in patients with growth hormone deficiency (Nyberg 2000). IGF-1, another anabolic hormone, improves mood in obese (Thompson et al 1998), but not non-obese (Friedlander et al 2001), postmenopausal women.

A rapidly evolving literature is highlighting the importance of neurosteroids other than DHEA in
the pathophysiology and treatment of anxiety and depression. For example, social isolation in rats significantly decreases brain and plasma levels of the GABA-A receptor agonist neurosteroids, allopregnanolone and THDOC, while significantly increasing levels of corticosterone; these changes are accompanied by increased "anxiety"-like behaviours (Serra et al 2000). Decreasing concentrations of allopregnanolone may be especially problematic in the face of chronic stress, since allopregnanolone can re‐strain the glucocorticoid response to stress (Guo et al 1995), and since allopregnanolone can protect against glutamate hippocampal neurotoxicity (Frank and Sagratella 2000). In humans, levels of allopregnanolone are low in depressed patients, and serotonin specific reuptake blocker (SSRI) antidepressant treatment increases CSF levels of this hormone, in direct proportion to the antidepressant effect (Uzunov et al 1998; Uzunova et al 1998). In addition to allopregnanolone, pregnenolone, THDOC and androsterone are promising neurosteroid targets for novel antidepressant or neuroprotective agent development (Barrot et al 1999; Frank and Sagratella 2000; George et al 1994; Maurice et al 1999; Meieran et al In Review; Patchev et al 1997; Rupprecht and Holsboer 1999a; Urbanoski et al 2000).

Behavioural treatment approaches to depression and hormonal dysregulation

To the extent that altered stress hormone secretion underlies or perpetuates depressive symptoms and physical illness, behavioural as well as pharmacological interventions that normalize the hormonal milieu should prove therapeutic (Cohen 2000; Dragan et al 1994; Sapolsky 1993). In fact, behavioural approaches to decreasing stress and arousal (e.g., decreasing "demand" while increasing predictability, control and feedback) might prove superior in the long run to the pharmacological approaches outlined above, since pharmacological strategies tend to "clamp" hormonal activity at either a low or high state and thereby reduce responsiveness to environmental demands (Sterling and Eyer 1988). Behavioral techniques, on the other hand, have the potential to increase flexibility and adaptability (Sterling and Eyer 1988). In the following section, we explore evidence for the hormonal mediation of some of the health benefits of "stress-reduction" and other behaviour treatment modalities. While most research in this area has focused on cortisol and DHEA, other stress-related neurosteroids may also mediate certain benefits of behavioural treatments, as discussed at the end of this section.

- **Decreasing cortisol**

Numerous studies have examined the effects of relaxation and stress-reduction techniques on cortisol and other stress-responsive hormones. Controlled studies of short-term interventions such as listening to music (Mockel et al 1994), biofeedback (McGrady et al 1987) or massage therapy (Field et al 1992; Field et al 1998) have shown decreases in cortisol levels; these reductions in cortisol levels were associated with improvements in anxiety and depression in some populations (Field et al 1998). Also, relaxation training (Cruess et al 2000) and cognitive-behavioural stress management therapies (Perna et al 1998) significantly lower cortisol levels, in direct proportion to decreases in negative affect and fatigue. Participants randomized to an 18-month comprehensive lifestyle intervention programme, compared to controls, showed normalization of initially elevated cortisol levels, in association with decreased body mass index, improvement in lipoprotein profiles and better overall health (Nilsson et al 2001). Experimental groups that learned to regularly meditate suppressed cortisol compared to controls (Gallos et al 1984; Jevning et al 1978; Sudsuang et al 1991); however, see Michaels et al (1979). Long-term meditators (average of 8.5 years) had 50% lower urinary free cortisol levels than a control group (Walton and Pugh 1995; Walton et al 1995), although these results are probably affected by selection bias. In a prospective four-month random-assignment study, meditators showed lower basal cortisol levels and slightly increased acute cortisol and growth hormone responses to stress (Maclean et al 1997). The biological significance of increased acute cortisol and GH responses to stress is unknown, but such rapid stress responses may indicate a more "healthy" allostasis. Finally, landing "controllability" to the experience of stress demonstrably lowers cortisol responses, even in healthy controls (Breier et al 1988; Cohen 2000).

As noted earlier, one mechanism by which cortisol over-exposure may lead to depression, cognitive impairment and/or hippocampal pathology is by decreasing hippocampal expression of BDNF (Duman et al 1997; Grundy et al 2000). It is unknown if stress reduction or behavioural interventions that lower cortisol levels, such as those discussed here, are capable of increasing BDNF levels, but in animals, physical exercise blocks stress-induced decreases in brain BDNF mRNA and increases adult hippocampal neurogenesis (Trejo et al 2001). These latter effects may be mediated by an increase in brain levels of the catabolic hormone, IGF-1 (Trejo et al 2001).

- **Increasing DHEA and neurosteroids**

Behavioural treatment programmes also significantly increase DHEA(S) levels. Cognitive-behavioural treatment of depressed patients increased urinary DHEA-S levels, in comparison to imipramine, which lowered levels (Tollefson et al 1990). In a prospective study, Army officers participating in a stress-reduction programme showed significant increases in DHEA-S levels
compared to non-participants (Littman et al. 1993). Similarly, Crues and colleagues (Crues et al. 1999) reported that 10 weeks of "cognitive-behavioural stress management" (comprised of treatments such as identification of cognitive distortions, assertiveness training, anger management, social support, group discussions, experiential exercises, progressive muscle relaxation, autogenic training, meditation and guided imagery), compared to a 10-week control "wait list" condition, significantly increased plasma DHEA-S levels and decreased cortisol-to-DHEA-S ratios in HIV-seropositive men. Treated subjects, compared to control subjects, also showed significant improvements in mood disturbance and perceived stress; these improvements were directly correlated with the decreases in plasma cortisol-to-DHEA ratios.

Consistent with these studies, Arnetz and colleagues (Arnetz et al. 1983) assigned elderly individuals from a senior citizen apartment building to either a "social enrichment" programme (e.g., study groups in botany, history, music and geography, as well as outings, picnics and visits to the opera and theatre) or to a programme of normal pre-existing activities for six months. The experimental group, compared to the control group, showed significant increases in DHEA, testosterone, oestradiol and GH levels, as well as significantly attenuated decreases in height (suggesting slowing of osteoporosis progression). The authors speculated that social isolation in the elderly decreases anabolic-to-catabolic hormone ratios, leading to increased susceptibility to illness (such as osteoporosis), and that social enrichment counteracts this process. Løkk (Løkk 1998) presented confirmatory data in an uncontrolled study of 17 non-demented geriatric day-care attendees who participated in a new rehabilitation programme designed to decrease the "stress of uncertainty and passivity" by giving patients greater control and responsibility over their own rehabilitation programmes. Patients were assessed at entry into the programme, after three months of treatment and again three months after discharge. Prolactin and cortisol levels significantly decreased over the three months of treatment, while DHEA and oestradiol levels significantly increased. These changes coincided with improvements in Activities of Daily Living ratings and with increases in "optimism" ratings. By three months after discharge from the programme, prolactin, cortisol and oestradiol levels had returned to pre-treatment levels, but DHEA levels remained elevated. In another prospective study, but one lacking a control group for the hormonal determinations, healthy adult participants in an "emotional self-management programme" experienced a 100% increase in salivary DHEA(S) levels; these levels were significantly correlated with the psychological variable "warmheartedness" (McCraty et al. 1998). Experienced practitioners of transcendental meditation (TM) were also found to have elevated DHEA-S levels (Glaser et al. 1992; Walton et al. 1995), generally comparable to the levels seen in non-practitioners 5-10 years younger, increased urinary 5-HIAA (the major 5-HT metabolite) levels and decreased urinary free cortisol levels compared to non-TM practitioners. The authors of the former report noted that extraneous factors, such as diet, body mass index and exercise, did not account for the difference in hormone levels (Glaser et al. 1992), and the authors of the latter report noted that DHEA-S levels in women varied directly with the months of TM practice (Walton et al. 1995). Music therapy and group drumming exercises were also found to increase DHEA-to-cortisol ratios in normal volunteers (Bittman et al. 2001). Lastly, as was the case with exercise effects on IGF-1 and on BDNF (discussed above), aerobic exercise training programmes can significantly increase serum DHEA levels (Boudou et al. 2000). In contrast to chronic or subchronic behavioural interventions, one session of Qigong training (a "stress coping" method) did not alter DHEA(S) or cortisol levels (Ryu et al. 1996).

An important therapeutic goal of cognitive-behavioural and other psychotherapies is increased perception of control over, and predictability of, life's aversive events (Sterling and Eyer 1988). Animal studies suggest one possible biochemical correlate of "controllability" that might bear upon its beneficial effects. Rats exposed to escapable shock, compared to non-shocked controls and to rats exposed to inescapable shock, showed a threefold increase in brain benzodiazepine-like substances (likely GABA-A agonist neurosteroids such as allopregnanolone or THDCC) and a marked protection against seizures induced by picrotoxin, a GABA-A receptor antagonist (Drugan et al. 1994). The authors concluded that the active behavioural "coping" and "stress control" these rats experienced led to the release of endogenous benzodiazepine-like compounds in brain which protected them from stress pathology (Drugan et al. 1994). This animal study raises the intriguing, but yet untested, possibility that cognitive-behavioural and other psychotherapies that are designed to increase one's sense of control and predictability might also increase brain allopregnanolone (or other GABAergic neurosteroids) levels in anxious or depressed patients, in a manner similar to that seen following serotonin antidepressant treatment (Uzunov et al. 1996).

- Clinical implications of behavioural treatment approaches

Stress reduction interventions usually reduce physiological arousal levels and lead to cognitive changes, such as increased perceptions of controllability and predictability. In these ways, they may have direct antidepressant effects as well as indirect ones by restoring balance to the
endocrine milieu (e.g., decreasing cortisol and increasing levels of DHEA or other anabolic hormones). In a complementary way, restoring cortisol and DHEA levels to normal may alter cognitive function and social behaviour in a direction less conducive to depression and to experiencing disappointing life events (Goodyer et al 1998). Interestingly, experiencing control or predictability over aversive events (Drugan et al 1994; Weiss 1972), or experiencing "environmental enrichment" (e.g., increased physical activity, social stimulation and learning experiences) (Meaney et al 1988; Mohammed et al 1993; Kempermann et al 1997), yields neurochemical and behavioural benefits that are not even seen in unstimulated animals. Indeed, in animals, exposure to environmental enrichment or to the mild stress of regular postnatal handling enhances cognition, attenuates age-associated hippocampal atrophy, induces nerve growth factor gene expression and BDNF mRNA expression in hippocampus, elevates expression of hippocampal glucocorticoid (Type II) receptors, enhances negative feedback efficiency of the LHPA axis and decreases glucocorticoid output (Meaney et al 1988; Mohammed et al 1993; Falkenberg et al 1992; Kempermann et al 1997). These findings in animals suggest that even relatively subtle, transient environmental or behavioural changes can have long-lasting impact on the brain and LHPA axis (Sapolsky 1993; Sterling and Eyer 1988; Jacobs et al 2000).

It remains unclear whether patients with initially disturbed LHPA activity are more or less likely to respond to behavioural interventions. However, behavioural treatments alone may be less appropriate for patients with clinically significant LHPA axis dysregulation. Thase and colleagues, for example, found that depressed inpatients with elevated urinary free cortisol levels showed poorer responses to cognitive-behavioural therapy (CBT) than did those with normal urinary free cortisol levels (Thase et al 1993; Thase 1994).

There is some evidence that stress reduction interventions like those described above also have direct impact on reducing physical disease or risk for disease (Castillo-Richmond et al 2000; Fahron et al 1987; Whitehouse et al 1996). Diabetic control, for example, may be an important target of behavioural "antiglucocorticoid" strategies. Diabetic glycemic control is often upset by stressful events, and decreases in cortisol levels may improve glycemic control by attenuating cortisol-induced insulin resistance. Biofeedback practiced over three months reduced blood sugar in adults with insulin-dependent diabetes, but the patients who were also depressed showed no benefit (McGrady and Horner 1999). However, in another recent study, a 12-week cognitive behavioural intervention for depression among patients with non-insulin dependent diabetes mellitus reduced depression and increased glycemic control at six months follow-up, compared to a control group (Lustman et al 1998). In preliminary data, reducing depressive and anxiety symptoms in Type II diabetics via stress reduction techniques also significantly reduces visceral fat up to six months later, compared to a control group (Epel et al 2001). These examples demonstrate the tight interplay between the LHPA axis, mood, and physical health. Treatments that affect common underlying causes of mood disturbance and allostatic load, such as improved anabolic balance, should theoretically be most effective.

Choice of antgliocorticoid drug and risk of side effects

Whereas the stress reduction and cognitive-behavioural techniques outlined here are already in routine clinical use, the pharmacological antiglucocorticoid approaches reviewed in this chapter remain largely experimental, and their full risk/benefit ratios remain to be determined. They are not yet recommended for routine clinical use (other than antiglucocorticoids in the treatment of Cushing's syndrome and DHEA in the adjunctive treatment of Addison's disease). A more detailed discussion of the clinical differences between existing antiglucocorticoid drugs and the risk of side effects with each one is presented elsewhere (Wolkowitz and Reus 1999).

Summary

The data reviewed here raise the possibility that antiglucocorticoid drug treatments or treatments that improve anabolic balance ameliorate depressive symptoms in some patients with major depression or other psychiatric disorders, and, additionally, can reduce certain physical signs of allostatic load. Such beneficial effects would be consistent with those observed in Cushing's syndrome patients treated with the same drugs. The majority of the reviewed treatment trials, however, were non-blinded or small-scale. Therefore, any conclusions at this point must be considered tentative. Behavioural techniques, which also normalize elevated cortisol levels and/or increase DHEA levels, have proven clinical efficacy, but whether their efficacy is mediated by their hormonal effects is unknown.

If this endocrinological model of depression and allostatic load is correct, it provides several novel sites for therapeutic intervention (Figure 3). "Biopsychosocial" interventions could be understood as having actions in common leading to normalization of stress hormone secretion, with attendant downstream normalization of neurotransmitter, neuropeptide and neurotrophin levels and restoration of the balance between catabolic and anabolic processes.

The studies reviewed here cumulatively suggest the dual importance of further studying anti-
glucocorticoid strategies in major depression and in other conditions characterized by allostatic load:
1. On a practical clinical level, it may lead to the development of novel pharmacotherapeutic approaches for certain psychiatric patients. In many of the reviewed studies, good responses to antiglucocorticoid agents were seen in patients refractory to traditional antidepressants. Improvements often occurred rapidly (as early as one to three weeks), and remission occasionally persisted for long periods of time (in some cases even after antiglucocorticoid treatment was stopped). Since a substantial proportion of depressed patients is resistant to or intolerant of traditional antidepressants, the availability of a new class of antidepressant medication would be significant.
2. On a theoretical level, it may lead to a better understanding of the role of dysregulation of the LHPA axis in major depression and other psychiatric disorders. This issue has been discussed and considered for over 45 years (Quarton et al 1955), but until the availability and use of relatively safe antiglucocorticoid drugs, no suitable paradigm has existed to test it. It may also help clarify whether neurotransmitter, neuropeptide and neurotrophin dysregulation and insensitivity to glucocorticoid negative feedback are primary or secondary pathological events in the development of depression. The well-replicated finding that persistent DST nonsuppression after antidepressant treatment portends poorly for long-term outcome (Ribeiro et al 1993) suggests that re-establishment of LHPA axis negative feedback may itself be an important therapeutic goal.

Further studies will be needed to determine the appropriate clinical role of antiglucocorticoids in psychiatric treatment and their role (as well as the role of certain behavioural interventions) in reducing the "allostatic load" sequelae of depression and other stressful conditions. Confirmation of antidepressant and health-promoting effects of the antiglucocorticoid drugs reviewed here would undoubtedly spur the development of safer compounds and would refine our notions of appropriate targets of pharmacotherapy. Elucidation of the relationship of hormonal normalization to clinical improvement might also lead to a laboratory "yardstick" by which to measure (and perhaps predict) incident clinical response to drug or psychotherapeutic interventions. The exciting recent developments in biological psychiatry and molecular biology that were reviewed in this article are undoubtedly harbingers of new treatments for depression, cognitive impairment and perhaps "brain aging" that lie on the horizon.

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References

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Cruess DC, Antoni MH, Kumar M, Ironson G, McCabe P, Fernandez


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Izuka H, Kishimotor A, Nakamura J, Mizukawa R (1996) Clinical...


leading to disease. Archives of Internal Medicine 153: 2093-2191.


Ruprecht R, Holboer F (1999a) Neuroactive steroids: Meca-
nisms of action and neuropsychoendocrinological perspectives.


Behav Brain Res 120: 87-95.


Sapolsky RM (2000a) Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 57: 925-935.


Wolf OT, Neumann O, H€llhammer DT, Gelben AC, Strasburger CJ, Dresend€rfer RA, Pi$ke KM, Kirschb€um C (1997) Effects of a two-week physiological dehydroepiandrosterone substitution on cog...


