Editorial
Commentary on the Nature and Treatment of Bipolar Disorder
Brian E. Leonard 110

Reviews/Mini-reviews
Stress Hormone-Related Psychopathology: Pathophysiologic and Treatment Implications
Owen M. Wolkowitz, Elissa S. Epel, Victor I. Reus 115

Original Investigations/Summaries of Original Research
A Serotonin Uptake-Stimulating Tetra-Peptide found in Urines from ADHD Children
Ying Liu, Karl-Ludvig Reichelt 144

Clinical Characteristics of Patients with Major Affective Disorders and Comorbid Migraine
Ole Bernt Fasmer, Ketil Joachim Oedegaard 149

Viewpoints
Past, Present and Future of Biological Psychiatry
Hans-Jürgen Möller 156

Case Reports/Case Series
Acne, Isotretinoin Treatment and Acute Depression
Chee Hong Ng, Mei Mui Tam, Stephen J Hook 159
It is estimated that the life-time prevalence of bipolar disorder is 0.6% in the United States and similar figures have been quoted for Europe and Australasia. It is also known that the risk of acquiring the disorder is increased in first degree relatives of affected individuals. Genetic linkage analyses have led to the identification of several regions in the human genome that may contain genes conferring susceptibility to the disorder. Nevertheless, specific genes that are highly associated with the acquisition of the disease have not so far been unequivocally identified (Stine et al 1997). The complex nature of the genetics of bipolar disorder might thus be explained by the interaction of multiple genes with environmental factors (Gershon 1989). The link between a genetic predisposition to bipolar disorder and specific neurotransmitter malfunction has arisen from the analysis of patients carrying associated RNA transcripts within the frontal cortex (Sun et al 2001). Thus the RNA transcripts which encode the serotonin transporter and components of the NK-kB transcription factor complex were shown to be increased in bipolar illness and also in some patients with schizophrenia. Such findings could be of fundamental importance in the understanding of the pathological basis of the disorder. In particular, the link between the serotonergic and immune systems could be of relevance to our understanding of the mechanisms whereby mood stabilising drugs act.

Lithium was one of the first drugs to herald the psychopharmacological revolution some 50 years ago, and it still remains one of the standard treatments for bipolar disorder. The complexity of action of lithium at the cellular level still remains an enigma despite all the advances in molecular neuroscience over the past decade. Undoubtedly the inability to patent lithium, combined with its success in the treatment of patients with bipolar disorder, contributed to the relative lack of interest of the pharmaceutical companies in the development of drugs to treat bipolar disorder. Thus neuroleptics to treat the acute symptoms of the disturbed patient, together with lithium for the long-term maintenance, largely formed the basis of the drug therapy for bipolar disorder for the past 40 years. Meanwhile, other areas of psychopharmacology developed at an astounding rate with the introduction of the novel antidepressants, antipsychotics and anxiolytics.

Despite the relative neglect of bipolar disorder by the pharmaceutical industry in the past, there has recently been a revival of interest for two main reasons. First because bipolar disorder is one of the few psychiatric conditions in which there is a genetic basis. In addition, its cyclical nature gave researchers the opportunity to study the transition from mania to depression, a situation which was not nearly so well defined in any other condition. Second, a number of psychotropic drugs were developed which were found to be therapeutically effective in the treatment of the disorder and which were superior to lithium in terms of their tolerability, safety and acceptability to the patient.

Despite the many advantages of the recently introduced mood stabilisers such as valproate and carbamazepine with regard to their reduced side effect profile, lithium still remains the most widely used drug in this category because of its proven efficacy (Baldessarini and Tordo 2000). Thus, after over 30 years of use in North America, and even longer in Europe, it continues to be the mainstay of treatment for the bipolar disorder, both for the treatment of the acute manic phase and for the prophylactic treatment of the disorder (Baldessarini and Tordo 2000). In addition to its ability to reduce the intensity and frequency of episodes of the illness, lithium has also been shown to reduce the excessive mortality that commonly occurs in patients with bipolar disorder (Nilsson 1999). This may be of relevance to the observed effect of lithium and some other mood stabilisers on aspects of the immune system which are grossly disturbed in bipolar disorder (McAdams and Leonard 1993).

Mood stabilisers and second signalling systems - cellular actions and therapeutic response

Despite the importance of lithium in the treatment of bipolar disorder, the cellular and molecular basis for its therapeutic effects remain uncertain. There have been innumerable studies of the effects of lithium in animals and in in vitro systems but the relevance of these studies to the pharmacological activity of the drug in man remains an enigma. As with most drugs used in psychiatric practice, lithium usually requires several weeks of treatment before it achieves optimum therapeutic efficacy. This precludes any simple mechanistic interpretations based on its acute biochemical effects. Indeed, it can be argued that the probable explanation for the mechanisms of action of all mood stabilisers is related to their effects on numerous biochemical pathways involved in the
regulation of mood rather than by targeting one or more neurotransmitter processes. For this reason, much recent research has focused on the second messenger systems and gene expression which occur distal to the changes in post-synaptic receptor function (Manji and Lennox 2000). Some of the neurotransmitters and neuromodulators that are affected by the chronic administration of lithium, and possibly other mood stabilisers, are shown in Table 1.

### Table 1

| Biochemical changes reported to occur following the chronic administration of lithium (Manji and Lennox 2000). |
|---|---|
| * Na/K ATPase |
| * Neurotransmitters - serotonin, noradrenaline, dopamine, acetylcholine, glutamate |
| * Neurotransmitter receptors - beta and alpha 2 adrenoceptors, dopamine D2 receptors, serotonin 1A receptors |
| * Signalling systems - phosphoinositides, G-proteins, phospholipase A2, adenylyl cyclase, calcium, protein kinase C, glycogen synthase kinase, myristylated alanine rich C kinase substrate (MARCKS), gene expression |

The mechanisms whereby the various neurotransmitters can be modulated by mood stabilisers to cause secondary changes to the signalling systems may be summarised as follows: Following the activation of the neuronal membrane-bound receptor by the appropriate neurotransmitter, the intramembrane G protein, which links the receptor to the second messenger systems, is activated and stimulates phospholipase C located within the neuron. This stimulates a cascade of changes involving the synthesis of inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 then stimulates the mobilisation of calcium ions which, together with the DAG, activates protein kinase C. Within the neuron there is a constant cycling of inositol phosphates and DAG. The concentration of myo-inositol in the neuron is critical for the efficiency of the second signalling system as it acts as the precursor of the phosphoinositides. At therapeutically relevant concentrations lithium has been shown to interfere with the inositol cycle by inhibiting inositol monophosphatase and inositol polyphosphatase 1-phosphatase, key enzymes involved in the recycling of inositol and inositol polyphosphates (Berridge et al 1982, 1989; Nahorski et al 1991). However, despite the attractive nature of this hypothesis, it is uncertain whether lithium treatment results in a reduction in the synthesis of intermediates in the phosphoinositide cycle which are the substrates for agonist-induced phosphatidylinositol turnover (Jope and Williams 1994). Furthermore, there is no evidence, despite the clinical observation that lithium reduces the concentration of myo-inositol in the brains of patients with bipolar disorder, that this action is associated with the therapeutic response to treatment (Jope and Williams 1994).

The protein kinase C (PKC) pathway has also been the subject of recent investigation as it is known to play a vital role in regulating pre- and post-synaptic neurotransmission (Manji and Lennox 2000). Quantitative autoradiography has demonstrated that chronic lithium administration results in a significant decrease in membrane-associated PKC in the hippocampus, and also in MARCKS protein, both of which have been implicated in regulating long-term neuroplasticity (Lennox et al 1992). The precise clinical relevance of these changes is uncertain but it is known that PKC isozymes are involved in the regulation of neuronal excitability and neurotransmitter release. As valproate produces similar effects to lithium (Lennox et al 1992) it can be hypothesised that mood stabilising drugs ultimately produce similar subcellular changes which may be relevant to their therapeutic actions. However, the precise sites of action of these drugs on the PKC pathway may differ, which may be reflected in the clinical observation that some patients show a preferential response to one mood stabiliser over another. If so, it may be possible to develop a new generation of mood stabilisers based on their ability to selectively inhibit PKC isozymes. In this respect, it is of interest to note that the anti-oestrogen tamoxifen acts as a potent PKC inhibitor and that preliminary studies show that it has anti-manic properties (Watson et al 1998).

Why don't mood stabilisers work immediately? The reason for the lag period in the therapeutic response, and the slow reversal of the therapeutic response when the mood stabiliser is abruptly stopped, has been the subject of much speculation. Despite the diverse nature of the mood stabilisers now available, there is no evidence that any of them act more rapidly than lithium. However at last
a consensus appears to be emerging in which the prolonged administration of such drugs is necessary to facilitate changes in gene expression. In this regard, the effects of lithium and valproate on the DNA-binding activity of some important transcription factors (in particular the activator protein-1 transcription factor family (AP-1)) has been studied. The AP-1 transcription factor is known to activate gene transcription in response to PKC activators, growth factors and cytokines, while the genes known to be regulated by the AP-1 family of transcription factors in the brain include those regulating neuropeptides, neurotrophins, neurotransmitter receptors and the enzymes concerned in the synthesis of neurotransmitters (Bebchuk et al 2000). Experimental studies have shown that both lithium and valproate, at therapeutically relevant concentrations, increase the activity of AP-1 transcription factors in rat brain \textit{ex vivo} (Hughes and Dragunow 1995). In addition, \textit{in vivo} studies have shown that chronically administered lithium increases the synthesis of tyrosine hydroxylase, the rate-limiting step in the synthesis of the catecholamines, in the frontal cortex, hippocampus and striatum (Manji et al 2001). Thus it may be hypothesised that following their chronic administration mood stabilisers, by increasing the expression of nuclear transcription regulating factors, change the plasticity of critical neuronal circuits, changes which underlie the clinical response to treatment. By their very nature, such adaptive effects can only occur following prolonged treatment.

\textbf{Mood stabilising drugs of the future}

Regulation of signal transduction and gene expression within critical regions of the brain can have profound effects on the biochemical events triggered by a range of different transmitters. Most types of mood stabilisers have been developed on the assumption that they alter one or more neurotransmitters which are presumed to be dysfunctional in bipolar disorder. Thus drugs which act either directly or indirectly on the classical neurotransmitters and their receptors are likely to be of limited overall benefit. This is of particular importance in the treatment of the therapy refractory bipolar patient in which, at present, mood stabilisers which directly target post-synaptic receptors appear to be effective, at least in some cases. In future, it is possible that drugs may be developed that target specific signalling systems (for example, the PKC isozymes) and either directly or indirectly increase the expression of neurotrophic factors. Thus mood stabilisers may owe their therapeutic benefits to their neuroprotective actions (Duman et al 1997) and therefore a future generation of mood stabilisers may be directly targeting molecules involved in critical neuronal survival and cell death. It is not without interest that lithium, which still remains the first-line treatment for bipolar disorder, affects not only a number of signalling mechanisms but also has a pronounced neurotropic action which may underlie its therapeutic activity. Valproate, widely accepted as an alternative to lithium, has qualitatively similar effects at the subcellular level. In contrast to lithium and valproate, carbamazepine appears to have a limited post-synaptic action. This may help to explain why carbamazepine is more limited than either of the former drugs in the treatment of bipolar disorder.

In conclusion, appraisal of the possible mechanisms whereby the conventional therapeutic agents are thought to act now opens the possibility for developing novel drugs which directly target secondary and tertiary signalling systems. By their neuroprotective and neurotrophic actions such drugs may assist in the remodelling of the neuronal structure of the brain and in this way improve the efficacy of treatment.

\textit{Brian E. Leonard}

\textit{Correspondence:}
Brian E. Leonard, Ph.D., D.Sc.
Department of Pharmacology
National University of Ireland
Galway
Ireland
Tel: +353 91 52 4411
Fax: +353 91 52 5700
E-mail: belucg@iol.ie
References


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, antiglucocorticoid, 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-glucocorticoid" effects (Brown 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 Eyer 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 Eyer 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 Eyer 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-glucocorticoid strategies in treating major depression and health outcome. In T. Jogin (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; Christeff 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-
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 1987b). 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 α, and β-adrenergic receptors as well as the sensitivity of NE receptor-coupled adenylate cyclase (De Kloet et al 1998). Such actions in the noradrenergic system may counteract antidepressant drug effects on β-adrenergic receptor responsiveness (Holsboer 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 5HT₁₅ 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 5HT₁₅ receptor mRNA levels and increased "depressive" behaviours such as decreased locomotion, decreased open-field behaviour and anorexia. After 5-7
days of stress exposure, however, the rats showed a normalization of corticosterone levels, 5HT$_{1A}$ receptor activity and behaviour. These presumably "adaptive" responses in 5HT$_{1A}$ 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 5HT$_{1A}$ 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 5HT$_{1A}$ 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 5HT$_{1A}$ 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$_A$ 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 1987; Zakon 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)"), tetrahydrodeoxycorticosterone (THDOC), androsterone, pregnenolone sulphate and allopregnanolone (all of which possess agonist or antagonist activity at brain GABA$_A$ and other receptors), may prove equally if not more important for maintenance.

![Figure 1](image_url)

**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 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 ischaemia, 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 (Muirialdo et al 2000). Indeed, in normal aging and in Alzheimer's disease, hippocampal perfusion (Muirialdo 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<sub>a</sub>, 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-I (Bastianetto et al 1999; Cardounel et al 1999; Kimonides et al 1998; Kimonides et al 1999; Mao and Barger 1998; Muirialdo 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 (Rasika et al 1999).

Chronically 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 SHT1, 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 SHT1, receptors (Jacobs et al. 1998; 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](image-url)

**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 key 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 (Raikkonen et al 2001), many 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.

**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). Depression 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 hypercortisolism 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 hypercortisolism 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 1999b; 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 activational or manic-like initially, they typically become more depressive in nature with continued steroid treatment (Pihlal 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; Ling et al 1981; Naber et al 1996; Varney et al 1984; Wolkowitz et al 1997a; Wolkowitz et al 1999b; Reus and Wolkowitz 1993; Boston Collaborative Drug Surveillance Program 1972). 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
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. It is 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 phenytoin (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 (Plihal et al 1996; Wolkowitz 1994; Wolkowitz et al 1997a). Endogenous states of glucocorticoid excess are discussed in the following sections.

**Endogenous glucocorticoid effects**

- **Cushing’s Syndrome**

** Neuropsychiatric syndromes**

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; Tretiowen 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 (invoking 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 Cushing's 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; Hamm 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 antiglucocorticoid 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 Cushing's syndrome patients and which also have neuroactive properties, such as DHEA, have received virtually no attention to date (Dubrovsky 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 (Dubrovsky 1991; Dubrovsky 1997). Further difficulty in interpreting the Cushing's syndrome literature is that patients with Addison's 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 (Arlt et al 1999; Arlt 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, antiglucocorticoid strategies (as well as pituitary or adrenal surgery) are also effective at reversing the physical complications of Cushing's syndrome. In fact, they may be more effective than traditional treatment targeted to individual somatic symptoms (Neto et al 2000). Antiglucocorticoid medication normalizes blood pressure, blood sugar control, hypokalemia, hirsutism and menstrual disturbances in the majority of Cushing's syndrome patients (Sonino et al 1991).

• Major depression and other conditions

Neuropsychiatric syndromes

Hypercortisolemia and resistance of the LHPA 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 behavioural 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 Cushing's syndrome patients, depressed patients may have hippocampal volume loss (Shah et al 1998; Sheline et al 1999; Sheline et al 1999; Wolkowitz et al 1990a). 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; Greden et al 1983; Ribeiro et al 1993; Zobel et al 1999), suggesting that LHPA 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 LHPA 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 1997; Heinz et al 1999; Piazza 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 1995; Iizuka et al 1996; Malison et al 1999; Murphy 1991a; Murphy 1991b; Murphy et al 1993; Murphy et al 1993; Murphy et al 1998; Murphy et al 1999; Murphy et al 1999; Murphy et al 1999a; Murphy et al 1999b; Wolkowitz et al 1999a; Wolkowitz et al 1999b; Wolkowitz et al 1999c), antidepressant effects were reported in at least some patients. Across the 12 studies reviewed, an average of 67.5% of the treated patients showed at least a partial antidepressant response, and 55% showed a "full" or clinically meaningful response. Of the studies that were single- or double-blinded, 50% of the treated patients showed at least some antidepressant effect.

![Figure 3](image-url)

**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.
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-deoxycorticisol and tetrahydrodeoxycorticosterone (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 1996). 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 hypercortisolism, 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).

- **Corticotropin releasing hormone (CRH) receptor antagonists**
  
  Elevated CSF CRH levels have been frequently described in depressed patients compared to controls (Nemeroff 1988; Nemeroff 2000), although in some studies (Kling et al 1991; Wong et al 2000), including an especially comprehensive one (Geracioti et al 1992), this finding was not replicated. It is possible that different subtypes of major depression (e.g., "typical" vs. "atypical") differ in patterns of CRH secretion (Gold and Chrousos 1985; Gold and Chrousos 1999; Kling et al 1989; Kling et al 1991). A compelling role can be posited for the aetiological involvement of CRH hypersecretion in symptoms such as anxiety, fear, over-arousal, decreased slow wave sleep, decreased eating and decreased libido (Gold and Chrousos 1985; Gold and Chrousos 1999; Holsboer 1988; Holsboer 1999; Holsboer 2000; Kling et al 1991; O’Brien et al 2001; Schulkin et al 1994).

To the extent CRH hypersecretion plays a pathophysiological role in the development or maintenance of anxiety or major depression, CRH receptor antagonists should be therapeutic (Holsboer 1999; O’Brien et al 2001; Owens and Nemeroff 1999). Rats and non-human primates administered the CRH-1 receptor antagonist, R121919/ NBI 30775 (“antalarmin”), show diminished anxiety, fear and lowered ACTH and corticosterone responses to novelty and intense social stress (Gutman et al 2000; Habib et al 2000). Early open-label human trials with CRH-1 receptor antagonists have suggested significant antidepressant and anti-anxiety effects in depressed patients (Holsboer 2000; Nemeroff 2000; Zobel et al 2000). The development of safe and effective CRH receptor blockers represents an important pharmaceutical goal (O’Brien et al 2001) and will provide an important tool for further studying the role of CRH hypersecretion in psychiatric and other stress-related illnesses.

- **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-
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 hypocortisolemia 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 hypocortisolemic 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) the 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 1990); (3) altering levels of other adrenal or neurosteroid hormones (e.g., shifting cholesterol metabolism in the direction of increased synthesis of certain GABA'ergic 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
humans, exogenous supplementation with DHEA are associated with depression, cognitive 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), postmenopausal women. 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 (Arlt et al 1999; Arlt 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 Jaggars 1999; Markowitz 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-Conner 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 1999a; Rabkin et al 2000), but effects in eugonadal patients with major depression are less clear (Margolese 2000; Seidman and Walsh 1999a). 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 restrain 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 1996; 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; Drugan 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 behavioural 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 (Crues 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 (Gallois et al 1984; Jeving et al 1978; Sudsuan 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" allostatics. Finally, lending "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 levels (Russo-Neustadt et al 2001) and increases adult hippocampal neurogenesis (Trejo et al 2001). These latter effects may be mediated via 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 (Tollefsen 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, Cruess and colleagues (Cruess 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. Lökk (Lökk 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. Pro lactin 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 pretreatment 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 such 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 "control- lability" 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 THDOC) 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 unstressed individuals. 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; Fahrion 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 antiglucocorticoid 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 hormone normalization to clinical improvement might also lead to a laboratory "yardstick" by which to measure (and perhaps predict) incipient 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.

Acknowledgements
The authors gratefully acknowledge support from the National Institute on Aging (Grant R41-AG13334-01), the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD), the Stanley Foundation of the National Alliance for the Mentally Ill (NAMI), the Scottish Rite Foundation and the UCSF Research Evaluation and Allocation Committee (REAC). We also gratefully acknowledge helpful discussions about antiglucocorticoid and DHEA treatments with Eugene Roberts, Ph.D. and Bruce McEwen, Ph.D., but the views presented here are not necessarily reflective of their own. Portions of this article are based on the chapter: "Antiglucocorticoid strategies in treating major depression and 'allostatic load'," by OM Wolko-witz, ES Epel and VI Reus, which appeared in: JH Thakore (ed) Physical Consequences of Depres-sion. Wrightson Biomedical Publ. Ltd., Peters-field, UK, 2001.

References


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


Rupprecht R, Holsboer F (1999a) Neuroactive steroids: Mecha-


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


Tolleson GD, Haus E, Garvey MJ, Evans M, Tuason VB (1990) 24 week physiological dehydroepiandrosterone substitution on cog-


A Serotonin Uptake-Stimulating Tetra-Peptide found in Urines from ADHD Children

Ying Liu, Karl-Ludvig Reichelt
Department of Pediatric Research, Rikshospitalet, Oslo, Norway

Summary
A tetra-peptide has been isolated from the urines of children with Attention Deficit Hyperactivity Disorder (ADHD) that we could not find in control urines. The tetra-peptide (G-S-E-N) stimulates the uptake of serotonin into platelets. The peptide may explain why serotonin is increased in platelets of ADHD children.

Key words: serotonin uptake, peptide, ADHD, platelets.

Correspondence:
Karl-Ludvig Reichelt, M.D., Ph.D.
Institute of Paediatric Research
University of Oslo
Rikshospitalet
0027 Oslo
Norway
Tel: +47 23 07 29 85
Fax: +47 23 07 27 80
E-mail: K.L.Reichelt@klinmed.uio.no

Introduction
One of the most frequently reproduced findings in ADHD (Attention Deficit Hyperactivity Disorder) is increased platelet serotonin (5HT) levels (Rogeness et al 1992; Shaywitz et al 1978). The reported decrease in 5-hydroxyindol acetic acid in cerebrospinal fluid in ADHD (Rogeness et al 1992; Shaywitz et al 1978) might reflect decreased availability of serotonin in the synaptic cleft, possibly caused by increased uptake or decreased release.

We have previously found increased levels of urinary peptides in ADHD (Hole et al 1988). We found a peptide-containing fraction which increased the uptake of serotonin into platelets (Hole et al 1988). We purified this factor and determined its structure by hydrolysis and amino acid analysis, sequencing, synthesis and co-chromatography of biological peptide with the synthetic compound, with peak augmentation on HPLC.

Reagents and methods

• Reagents
Reagents were analytical grade to sequence quality and from Sigma Chemicals, St Louis, Mo. if not specifically stated.

• Patients
Patients were all diagnosed by Prof. K. Hole and Prof. H. Kløve at the University of Bergen (Hole et al 1988) (Mean age 9.4 years ± 4.6, N = 20 urines). They all had to fulfil the following criteria:
1: Excessive hyperactivity or restlessness for age demonstrated by inability to sit still, up-and-down activity and fidgeting.
2: Difficulty of sustained attention demonstrated by inability to complete tasks, "forgetting" demands made by task, and easy distractibility in unstructured situations.
3: Impulsive behaviour shown by at least three of the following: a) Sloppy work in spite of efforts to perform; b) speaking out of turn and noise-making in class; c) frequent interruptions or intrusion into other children’s activities; d) difficulty of awaiting turn in games; e) low frustration tolerance; f) fighting with other children because of frustration intolerance.
4: Diminished sensitivity to reinforcement.
5: Duration at least 1 year.

It should be noted that two thirds of the children
were examined by skin conductance and showed decreased basal level and faster habituation to 1000 Hz 95 dB tones than the controls (Kløve and Hole 1979). None had Tourette syndrome or other known psychiatric syndromes. None of the children were on any drugs at the time, and had been drug-free for at least two weeks.

Our control population was made up of 140 children aged between one and 13 years, randomly selected from schools and kindergartens. None of the control children had been observed to show behavioural deviations. Mean age was 8.7 ± 4 years. Ten 24-hour urines from male patients were used as the starting material and run in parallel. Ten age-matched children delivered control urines also run in parallel. The examination had been approved by the ethics committee at the University of Bergen; all participants were volunteers and gave informed consent.

**Urine collection**
A complete 24-hour urine was collected by the parents at home and placed in the deep freeze, with thymol in ethanol (0.01g/l) as a preservative.

**Platelets**
Platelets were obtained from healthy post-pubertal male volunteers working in our laboratory, and prepared as described (Pedersen and Reichelt 1988). Males were used because female platelets change with the menstrual cycle (Pedersen and Reichelt 1988). Furthermore, we do not know if there are changes in the serotonin uptake protein per se or the serotonin receptor in ADHD. Nor do we know what level of this peptide might be bound at any time in vivo. Therefore we used normal controls as platelet donors. Because the Fura-2 calcium marker leaked out of platelets that were cooled to 4°C during preparation, and the responsiveness to agonists was poor, the platelets were prepared in the presence of citric acid/dextrose (65mM citric acid, 85mM Na-citrate,111mM glucose), made as described (Pedersen et al 1994). Briefly described, blood was drawn by cubital venepuncture into one sixth the volume of citric acid/dextrose (65mM citric acid, 85mM Na-citrate,111mM glucose), made as described (Pedersen et al 1987). Platelet-enriched plasma (PRP) was obtained by centrifugation at 800 x g for 5 minutes at 20°C (Pedersen and Reichelt 1988; Pedersen et al 1994). Briefly described, blood was drawn by cubital venepuncture into one sixth the volume of citric acid/dextrose (65mM citric acid, 85mM Na-citrate,111mM glucose), made as described (Pedersen et al 1987). Platelet-enriched plasma (PRP) was obtained by centrifugation at 800 x g for 5 minutes at 20°C. The platelets were then precipitated by centrifugation at 1000xg for 8 minutes at the same temperature, and re-suspended in a modified buffer (NaCl 140, KCl 5, MgCl, 1, NaHPO, 1, Glucose 10 and HEPES 10 all mM) at pH 7.54. Na-Pyruvate (10mM) and malate (10mM) were added to prevent ATP depletion. Platelets were counted on a Coulter counter and the number of platelets was adjusted to 1.5x 10⁸ platelets per ml by appropriate dilutions in buffer.

**Serotonin uptake**
Platelets were prepared as outlined above. The re-suspended platelets were divided in aliquots of 450 micro-liters and stored at 4°C until used and then pre-incubated for 5 minutes at 37°C. The aliquots were then incubated with various concentrations of the peptides in 25 µl buffer and incubated for 4 minutes, and after 2 minutes (°C)-5-HT (Amersham Life Science Comp, UK) in 25 µl was added to a final concentration of 1nM and 41530cpm (Lingjaerde 1969). Serotonin uptake ran for 2 minutes, during which time the uptake is still linear. The reaction was stopped by 3 ml ice-cold isotonic saline and rapid cooling in an ice bath. The samples were then centrifuged at 400 x g for 15 minutes at 4°C and washed with 3 ml isotonic ice cold saline and re-centrifuged. 0.5 ml of distilled water was added to the precipitate to make the platelets burst by osmotic swelling. The uptake of label into the platelets was determined by liquid scintillation in Ultima Gold™ XR reagent (Packard Instrument Comp Inc. Downers Grove, Illinois) and counted in a Model TriCarb 2300TR Scintillation Spectrometer. All samples were run in triplicate or more, and passive uptake was subtracted by using a 0°C blank. Quenching was controlled for by neighbouring channel ratio and external standard.

**Peptide purification**
Peptide purification followed the outline that has been extensively described (Gembitsky et al 1998) and is presented in the sequence in which the systems were used. Chromatographic buffers were removed between each run by freeze-drying material corresponding to any given peak eluted. Briefly, starting with batches of urine in parallel, peptides were separated from amino acids, ammonia and salts by 50 micron C-18 reverse phase preparative column chromatography of 2.6x40 cm (Bohlen et al 1980). Protonable peptides were separated from non-protonable peptides (mostly N-substituted) by cation exchange (AG50Wx8,400 mesh from Bio Rad Labs, Richmond California of dimensions 1x 40 cm) with counter ion H⁺. This was followed by anion exchange on AG 1 x1 (200-400 mesh) of dimensions 1x40 cm with counter ion acetate to separate strongly anionic peptides from neutral and basic peptides (Reichelt et al 1987). Approximate molecular weight (MW) was found by gel filtration on a Fractogel MG-2000 column 1.6x 90 cm, from Merck (Darmstadt, Germany), in 1 M acetic 40mM HCl buffer with a flow rate of 4 ml per 10 minutes and collecting of 4 ml fractions. The following HPLC systems were used with a column of Partisil M9 10/25 ODS (Whatmann): Trifluoroacetic acid (TFA) 10mM with n-propanol from 0-48% over 60 minutes gradient and detection at 215 nm; TFA with acetonitril gradient from 0-60% by volume over 60 minutes and 215nm detection; Hepta-fluoro-buturate 5 mM and acetonitril from 0-40 % by volume over 40 minutes and detection at 215 nm. Straight phase separation isocratically in 2.5% H₂O in acetonitril was run on TSK 80 amide column 4.4 mm x 25 cm from Tosoh, Japan (Yoshida
1997) and 215 nm detection. Final purification was run using Vydac C-18 reverse phase columns (Hesperia, Ca 92345, USA) 5µm 0.1x25 cm developed in TFA 10mM and 0-30% linear gradient by volume acetonitril and detection at 215 nm.

Flow rate was 1 ml / min in all HPLC systems used with gradient mixer from LDC and detector sensitivity of the LDC UV detector (Laboratory Data Control, Riviera Beach, Fl., USA) of 0.1.

• Peptide structure
Hydrolysis of the peptide in 6M HCl with a trace of phenol in closed vials for 12 hours and removal of acid over KOH pellets and P2O5 in vacuum. The hydrolyzed amino acids were analyzed on the Alpha plus amino acid analyzer (Pharmacia, Uppsala Sweden). To check for UV-absorbing compounds, absorption was checked from 215 to 320 nm in aqueous solution. Sequencing was done by combining Edman with dansylation (Reichelt et al 1987). The proposed peptide was synthesized by Peninsula Labs, Belmont, Ca, on a commercial basis. Analogues were also synthesized by Bachem., Bubendorf, Switzerland. Co-chromatography with biological samples was carried out in all the HPLC systems described.

Results
The bioactivity eluted in the organic phase on the initial C-18 reverse phase separation. The purification showed that the compound was ninhydrin colourable and retained on cation exchanger, and not retained on an anionic ion exchanger in the acetate form. It did not absorb UV light at 280nm and it was of low MW (Kav = 0.32, N =10). C-terminally amidated peptides show an apparent molecular size larger than the de-amidated peptides (Reichelt et al 1987). Figure 1 shows the results of testing the first HPLC fractions, where Ctr’s are controls. Fraction B is the active peptide containing fraction eluting at 16 ml on the first HPLC run. C to D are inactive peptide peaks eluting later than B and found in this purification step. H is the effect of hydrolyzed fraction B. On Vydac C-18 the peptide eluted as early as 4 ml. On straight phase, as described, the peptide appeared at 16 ml. The last purification step resulted in a peptide with Glu:Asp:Ser:Gly in the ratio (taking Glu=1) of 1:1:0.8:1.2 (average of three hydrolysates), and an increase in NH3. The N-terminal amino acid was Gly and the next amino acid Ser, and the third Glu. The Gel filtration data fit a monomer (tetra-peptide), and because we found only 1 N-terminal amino acid, the peptide was considered pure. The hydrolyzed peptide was inactive.

The peptides Gly-Ser-Gln-Asp, Gly-Ser-Glu-Asn, Gly-Ser-Gln-Asn were made. Gly-Ser-Gln-Asp and Gly-Ser-Gln-Asn were active but only at a very much higher concentration, only Gly-Ser-Glu-Asn co-chromatographed completely and showed activity at very much lower concentrations (Table 1). For 12 paired experiments, the Wilcoxon paired test had values of T+=1, T-=77, p=0.0033 two-tailed. The lower the serotonin uptake in controls, the higher the stimulation (not shown). At these higher concentrations their effects could be due to molecular mimicry, but also indirect effects such as peptidase inhibition (La Bella et al 1985) protecting any endogenous peptide if present against breakdown. Peptidases are quite abundant at the surface of cells and platelets. Better stimulation and less changes of uptake over an experiment were obtained when the platelets were stored on ice in spite of leaking Fura 2.

We therefore propose that Gly-Ser-Glu-Asn may be one of the serotonin uptake stimulating peptides in ADHD. The peptide showed bell-shaped dose response and only the 10^-10 to -10 M were statistically different as shown. With the pure peptide the stimulation is not large but varies from 5.8% to 33%. However, if inactive peptide is added in then we could regain higher activity similar to that shown in Figure 1. We think this may be due to the fact that peptides generally inhibit peptidases and hence protect the pure peptide from breakdown (La Bella et al 1985).

Scrambled peptides like Ser-Gly-Glu-Asn and Ser-Gly-Asp-Gln were inactive (not shown). The pure biological and synthetic peptide had somewhat lower activity than the impure one. This could likewise be due to protection by contaminant peptides against breakdown by peptidases.
We could not recover this peptide from ten 24-hour batches of normal urine run in parallel. We found the peptide in two out of 10 examined 24-hour urines from autistic children of the same age range, but in marginal quantities. No sequence was performed on these peptide fractions, only co-chromatography with peak augmentation.

Table 1

<table>
<thead>
<tr>
<th>Peptide:</th>
<th>G-S-E-N</th>
<th>G-S-E-N</th>
<th>G-S-Q-N</th>
<th>G-S-Q-D</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal conc:</td>
<td>10-10</td>
<td>10-9</td>
<td>10-5</td>
<td>10-5</td>
<td>--</td>
</tr>
<tr>
<td>C.P.M. increase</td>
<td>2408</td>
<td>2501</td>
<td>2068</td>
<td>2070</td>
<td>1853</td>
</tr>
<tr>
<td>SD</td>
<td>55</td>
<td>57</td>
<td>52</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>P</td>
<td>0.006</td>
<td>0.006</td>
<td>0.02</td>
<td>0.03</td>
<td>--</td>
</tr>
<tr>
<td>Percent</td>
<td>30</td>
<td>31</td>
<td>11</td>
<td>12</td>
<td>--</td>
</tr>
</tbody>
</table>

Serotonin (5-HT) uptake into platelets as described in methods. Only G-S-E-N showed complete co-chromatography in all HPLC systems used. The analogues only show effect at very high concentrations, which may be due to molecular mimicry or indirect effects due to peptidase inhibition (LaBella et al 1985). 40 000 cpm = 1 nanomole 5-HT. The uptake is quantitatively similar to published data (Lingjærde 1969) except that we only have 1-8 platelets and incubate for 2 minutes to ensure linearity of uptake.

The biological peptide showed an increase at –10 molar of 2555± 61 (n=10). The effect of optimal concentration of synthetic peptides on serotonin uptake in platelets

The effect of optimal concentration of synthetic peptides on serotonin uptake in platelets

Discussion

Increased levels of serotonin in platelets is one of the more reproducible findings in ADHD (Rogeness et al 1992; Shaywitz et al 1978). Decrease in serotonin in the synaptic cleft due to increased uptake would cause impulsive behaviour and hyperactive, aggressive behaviour, as seen in hypo-serotonergic animal models (Rogeness et al 1992).

We have found a tripeptide from normal plasma and the urine from some autistic children with the structure PyroGlu-Trp-GlyNH2, bell-shaped dose response (Pedersen et al 1999). This peptide stimulated the serotonin transporter in hamster ovarian cells (two- to threefold over baseline) (Keller 1998). The tripeptide doubled the serotonin content of the platelets when injected into pups sub-cutaneously (Persico et al 1998), while the present tetra-peptide only increased the level by 30 to 50% (Persico et al 1998). We do not know if this is a factor similar to that found earlier (Angel and Paul 1984).

Increase in peptides in serum and urine is usually secondary to peptidase defects or peptidase inhibition (Watanabe et al 1993). Peptides are excellent inhibitors of peptidases in general (LaBella et al 1985), therefore peptidase inhibition is also a possibility in states of hyperpeptidemia and -uremia (Asano et al 1991; Abassi et al 1992).

The tetra-peptide is found in the C-terminal part of alpha1-casein (residues 87-90). In normal persons a milk protein-containing meal causes considerable quantities of peptides to move to the blood (Chabance et al 1998), which are rapidly broken down. We have previously demonstrated an increase in bovine casomorphins in autism and schizophrenia (Reichelt et al 1991; Reichelt and Reichelt 1997), so that the peptide reported here may also be an alimentary peptide. Whether this can explain the frequent association of milk intolerance to ADHD (Egger et al 1985; Egger et al 1992; Carter et al 1993; Schmidt et al 1997; Breakey 1997) is unknown. However, because serotonin is critical to synaptic genesis and maintenance of synapses in the central nervous system (Chen et al 1994; Okado et al 1993; Whittaker-Azmitia and Azmitia 1994), the peptide may be important to the pathophysiology of ADHD and some cases of autism. Furthermore, decreased 5-hydroxyindol acetic acid in CSF found in ADHD (Rogeness et al 1992) could be caused by increased pre-synaptic uptake.

Acknowledgements

This project is supported by EU grant BMH4-CT96-0730 (Coordinator Prof. Dr. F Keller). The authors are grateful to the Sommer’s foundation for support in the synthesis of peptides, and to the Seim family foundation for wages for a technician.

References


LaBella FL, Geiger JD, Glavin GB (1985) Administration of peptides inhibit the degradation of endogenous peptides. The dilemma of distinguishing direct from indirect effects. Peptides 6: 645-660.


Clinical Characteristics of Patients with Major Affective Disorders and Comorbid Migraine

Ole Bernt Fasmer, Ketil Joachim Oedegaard
Department of Psychiatry, University of Bergen, Bergen, Norway

Summary
The present study was undertaken to examine the clinical characteristics of patients with major affective disorders and comorbid migraine. Patients (n = 102) with an index episode of either major depression or mania were interviewed with a semi-structured interview based partly on DSM-IV criteria and partly on Akiskal’s criteria for affective temperaments. Compared to the patients without migraine (n = 49), the patients with comorbid migraine (n = 53) had a higher frequency of bipolar II disorder (43% vs. 10%), a lower frequency of bipolar I disorder (11% vs. 33%), an approximately equal frequency of unipolar depressive disorder (45% vs. 57%) and a higher frequency of affective temperaments (45% vs. 22%). The migraine patients also had a greater number of anxiety disorders (3.0 vs. 1.9) and a higher frequency of panic disorder and agoraphobia. Gender distribution, age, age at onset of first affective episode, number of previous episodes and symptoms during depressive episodes were similar in both groups. Based on these findings it is suggested that the presence of migraine may be used to delineate a distinct subgroup of the major affective disorders.

Key words: bipolar disorder, depressive disorder, migraine.

Introduction
Both migraine and depression are common disorders in the general population, with a comparable prevalence (around 10%) and a similar gender distribution, females being more often affected than men (Thase and Kupfer 1996; Silberstein and Lipton 1993). Both disorders have a genetic background, but for none of them has it been possible to pinpoint a single genetic locus (Gelernter 1995; Gardner 1999). Case series and uncontrolled studies have shown a strong association between migraine and affective disorders, and this has been confirmed in epidemiological studies (Breslau et al 1994; Swartz et al 2000). The risk of experiencing episodes of major depression is increased threefold among migraine sufferers, and they also have an increased frequency of both bipolar I and II disorders (Breslau et al 1994). Furthermore, there is also a strong association between migraine and anxiety disorders (Breslau et al 1994; Marazziti et al 1999; Swartz et al 2000). Family studies have suggested that there is a syndromal relationship between migraine, depression and anxiety disorders (Merikangas and Stevens 1997). The most frequent pattern is an early occurring anxiety disorder followed by migraine and major depression.

There is a paucity of studies of migraine in patients presenting primarily with psychiatric disorders. Endicott (1989) found in a study from private specialist practice in New York that between 20 and 50% of patients with major affective disorders also had migraine, and Mahmood et al (1999) found a 26% prevalence of migraine in patients with bipolar disorders. We have previously reported that in patients hospitalized for major affective disorders approximately one half had comorbid migraine, and among those with migraine one half had unipolar depressive disorder and one half bipolar disorders. Most of the bipolar patients had bipolar II disorder (Fasmer Submitted). There is, however, little information concerning the characteristics of the affective disorders in patients with comorbid migraine. Merikangas and Stevens (1997) have stated that the depressive episodes often have an atypical symptom pattern. The purpose of the present study was to study more closely the type and characteristics of the affective disorders in patients with major affective disorders and comorbid migraine.

Material and methods
The study group consisted of 102 patients from
one of the university hospitals of Bergen. Sixty-two subjects were consecutively admitted patients to a 12-bed open psychiatric ward. The frequency of migraine in these patients is presented in a previous paper (Fasmer Submitted). The remaining patients were inpatients at other psychiatric wards \( (n = 19) \) or were recruited from the psychiatric outpatient department or day-care unit \( (n = 21) \). Patients were included if they had a major affective syndrome (major depression or mania) that was not clearly secondary to an organic or substance abuse disorder, were between 18 and 65 years old, and gave informed consent to participate. Patients were excluded if they did not speak Norwegian with sufficient fluency to be interviewed without an interpreter. The patients who were psychotic at admission were not psychotic when interviewed. All interviews were conducted by the same investigator. The local ethics committee had approved the study protocol.

We used a semi-structured interview based on DSM-IV criteria (American Psychiatric Association 1994) for affective disorders (major depressive episode, mania, hypomania), anxiety disorders (panic disorder, agoraphobia, specific phobia, social phobia, generalized anxiety disorder, obsessive compulsive disorder) and eating disorders (anorexia nervosa and bulimia nervosa). Hyperthymic, irritable and depressive temperaments were diagnosed according to the criteria of Akiskal and Mallya (1987), and cyclothymic temperament according to Akiskal and Akiskal (1992). Criteria for the cyclothymic temperament requires at least three of five attributes of each of the following two sets, with an indeterminate early onset (<21 years). First group: 1. Hypersonmia versus decreased need for sleep; 2. Introverted self-absorption versus uninhibited people-seeking; 3. Taciturn versus talkative; 4. Unexplained tearfulness versus buoyant jocularity; 5. Psychomotor inertia versus restless pursuit of activities. Second group: 1. Lethargy and somatic discomfort versus eutonia; 2. Dulling of senses versus keen perceptions; 3. Slow-witted versus sharpened thinking; 4. Shaky self-esteeem alternating between low self-confidence and overconfidence; 5. Pessimistic brooding versus optimism and carefree attitudes. The hyperthymic temperament requires at least five of the following characteristics, with an indeterminate early onset (<21 years): 1. Irritable, cheerful, overoptimistic, or exuberant; 2. Naive, overconfident, self-assured, boastful, bombastic, or grandiose; 3. Vigorous, full of plans, improvident, and rushing off with restless impulse; 4. Over-talkative; 5. Warm, people-seeking, or extroverted; 6. Over-involved and meddlesome; 7. Uninhibited, stimulus-seeking, or promiscuous. The irritable temperament requires at least five of the following characteristics, with an indeterminate early onset (<21 years): 1. Habitually moody, irritable and choleric, with infrequent euthymia; 2. Tendency to brood; 3. Hypercritical and complaining; 4. Ill-humoured joking; 5. Obtrusiveness; 6. Dysphoric restlessness; 7. Impulsive. The depressive temperament requires at least five of the following characteristics, with an indeterminate early onset (<21 years): 1. Gloomy, pessimistic, humourless, or incapable of fun; 2. Quiet, passive, and indecisive; 3. Sceptical, hypercritical, or complaining; 4. Brooding and given to worry; 5. Conscientious or self-disciplining; 6. Self-critical, self-reproaching, and self-derogatory; 7. Preoccupied with inadequacy, failure, and negative events to the point of morbid enjoyment of one's failures.

Unipolar depressive (major depressive disorder) and bipolar I disorders were diagnosed according to DSM-IV criteria. Bipolar II disorder was in this study defined to include patients fulfilling either DSM-IV criteria for the disorder or the criteria for a cyclothymic or hyperthymic temperament as described above, in addition to one or more major depressive episodes.

In addition the following information was recorded: age at onset of the first major affective episode and the first depressive episode, the number of depressive episodes, the presence of melancholic or atypical symptoms (DSM-IV criteria) in the present or in previous episodes, seasonal variability of depressive episodes, current or previous suicide attempt, psychotic symptoms, and the presence of prominent irritability or suspiciousness in the current or previous major depressive episodes.

Symptoms of the following psychiatric disorders were also recorded (DSM-IV criteria): attention-deficit/hyperactive disorder, learning disorders and abuse of alcohol and drugs. Use of tobacco currently or previously was noted. History of characteristic symptoms of the following somatic symptoms were asked for: allergic rhinitis or other allergic disorders, asthma or atopic eczema, Raynaud syndrome (Miller et al 1981) and thyroid disorders. Hand-preference was assessed according to the method of Oldfield (1971).

The criteria of the Headache Classification Committee of the International Headache Society (1988) were used to establish the diagnosis of migraine. In addition to migraine with and without aura, the occurrence of migraine auras without headache was specifically recorded.

Information about serious psychiatric disorders (major depression, bipolar disorder, psychosis, suicide) or migraine in first degree family members was obtained from interviews of patients or from hospital records.

Chi-square test or t-test (two-tailed) were used to calculate differences between groups, with a significance level of 0.05. SPSS version 9.0 was used for the statistical analyses.
Results

The mean age of the patients was 38.5 ± 9.6 years (range 19 - 64). Sixty-nine per cent were female. The index episode was depression in 88% of the patients and mania in 12%. During the index episode 79% of the patients were inpatients. Fifty-three patients had migraine; 25 patients had migraine with aura, 18 had migraine without aura, and 10 had migraine aura without headache. Most of the patients did not present migraine headaches as a prominent complaint when interviewed and often a history of migraine was not noted in the hospital records. The age at onset of migraine was 21.0 ± 10.3 years (mean ± SD, range 5 - 44). Characteristics of the sample, grouped according to the presence or absence of migraine, are detailed in Table 1. There were no significant differences in age, age at onset of first major affective episode, gender distribution, marital status, work activity, alcohol or substance abuse or family history of serious psychiatric illness. As expected there were more patients in the migraine group with a family history of migraine.

Table 1
Characteristics of the sample (n = 102)

<table>
<thead>
<tr>
<th>Migraine (n = 53)</th>
<th>No migraine (n = 49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>38.5 ± 8.8</td>
<td>38.5 ± 10.4</td>
</tr>
<tr>
<td>First affective episode (years, mean ± SD)</td>
<td>26.9 ± 10.9</td>
<td>27.3 ± 9.9</td>
</tr>
<tr>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>74 (39)</td>
<td>63 (31)</td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>40 (21)</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Holding a job or studying</td>
<td>57 (30)</td>
<td>55 (27)</td>
</tr>
<tr>
<td>Use of tobacco</td>
<td>87 (43)</td>
<td>76 (37)</td>
</tr>
<tr>
<td>Alcohol or substance abuse</td>
<td>36 (19)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Serious psychiatric illness in family</td>
<td>60 (32)</td>
<td>51 (25)</td>
</tr>
<tr>
<td>Migraine in family</td>
<td>49 (26)</td>
<td>18 (9)</td>
</tr>
</tbody>
</table>

NS: Not significant 1 T-test (two-tailed) 2 Chi-square test

In Table 2 the distribution of affective disorders are shown. The frequencies of unipolar and bipolar disorders were similar in patients with and without migraine. However, in the migraine group most of the bipolar patients had bipolar II disorder, while in the group without migraine most of the patients had bipolar I disorder. Seventeen of 28 bipolar II patients fulfilled the DSM-IV criteria for the disorder and 11 were diagnosed on the basis of a cyclothymic (n = 9) or a hyperthymic (n = 2) temperament without having had discrete hypomanic episodes. There was also a significantly higher frequency of affective temperaments in the migraine group. Among the migraine patients 21% had a cyclothymic, 9% a hyperthymic and 15% a depressive temperament, while in the group without migraine 12% had a cyclothymic, 2% a hyperthymic and 8% a depressive temperament. In the whole sample no patients had an irritable temperament.

Table 2
Affective disorders

<table>
<thead>
<tr>
<th>Migraine (n = 53)</th>
<th>No migraine (n = 49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unipolar depressive disorder</td>
<td>45 (24)</td>
<td>57 (28)</td>
</tr>
<tr>
<td>Bipolar II disorder</td>
<td>43 (23)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>11 (6)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Affective temperament</td>
<td>45 (24)</td>
<td>22 (11)</td>
</tr>
</tbody>
</table>

NS: Not significant Chi-square test

In Table 3 the characteristics of the depressive episodes are shown. The only differences that emerge between the groups are the frequencies of irritability and suspiciousness, which were higher in the migraine group. There were no differences in the frequency of psychotic symptoms and, when separating these symptoms into mood congruent and incongruent, there were again no differences (data not shown).

In Table 4 the characteristics of the depressive episodes are shown. The frequencies of anxiety and eating disorders are shown in Table 3. In the whole sample the frequency of anxiety disorders was high and, when comparing number of patients with and without any anxiety disorder in the two groups, the difference was not significant. However, when counting the number of anxiety disorders for each patient the migraine patients had a significantly greater number of anxiety disorders. The age at onset of the first anxiety disorder was 14.5 ± 8.6 (mean ± SD) for the patients with migraine. This was earlier than the onset of migraine, which again was earlier than the onset of the first depressive episode. For 59% of the patients with migraine and anxiety disorders the first anxiety disorder started before the migraine, and in 63% of the cases the first episode of major depression occurred after the onset of migraine. The first anxiety disorder was most often a specific phobia. In 16 patients the specific phobia occurred before the onset of migraine and in 11 after the onset of migraine. The similar figures for panic disorder were nine before and 15 after the onset of migraine, and for agoraphobia 11 and 17, respectively. The age at onset of the different anxiety disorders did not differ significantly between patients with and without migraine (data not shown).
frequencies of melancholic and atypical features of the depressive episodes were very similar and, when considering the specific symptoms of guilt and rejection sensitivity separately, they did not differ significantly (data not shown).

Table 3

<table>
<thead>
<tr>
<th>Anxiety and eating disorders</th>
<th>Migraine (n = 53)</th>
<th>No migraine (n = 49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of anxiety disorders</td>
<td>3.0 ± 1.8</td>
<td>1.9 ± 1.7</td>
<td>0.003¹</td>
</tr>
<tr>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>91 (48)</td>
<td>78 (38)</td>
<td>NS²</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>51 (27)</td>
<td>24 (12)</td>
<td>0.006²</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>58 (31)</td>
<td>27 (13)</td>
<td>0.001¹</td>
</tr>
<tr>
<td>Social phobia</td>
<td>47 (25)</td>
<td>35 (17)</td>
<td>NS³</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>49 (26)</td>
<td>45 (22)</td>
<td>NS³</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>57 (30)</td>
<td>47 (23)</td>
<td>NS³</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>28 (15)</td>
<td>16 (8)</td>
<td>NS³</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>17 (9)</td>
<td>4 (2)</td>
<td>0.036²</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>11 (6)</td>
<td>6 (3)</td>
<td>NS⁴</td>
</tr>
</tbody>
</table>

NS: Not significant ¹ T-test (two-tailed) ² Chi-square test

Table 4

<table>
<thead>
<tr>
<th>Characteristics of major depressive episodes</th>
<th>Migraine (n = 52) *</th>
<th>No migraine (n = 46) *</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset first depressive episode (years ± SD)</td>
<td>26.5 ± 10.6</td>
<td>27.5 ± 9.6</td>
<td>NS³</td>
</tr>
<tr>
<td>Number of depressive episodes</td>
<td>5.7 ± 5.9</td>
<td>4.0 ± 4.3</td>
<td>NS³</td>
</tr>
<tr>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonal variability</td>
<td>30 (16)</td>
<td>20 (9)</td>
<td>NS³</td>
</tr>
<tr>
<td>Psychomotor symptoms</td>
<td>38 (20)</td>
<td>37 (18)</td>
<td>NS³</td>
</tr>
<tr>
<td>Melancholic features</td>
<td>40 (21)</td>
<td>35 (17)</td>
<td>NS³</td>
</tr>
<tr>
<td>Atypical features</td>
<td>40 (21)</td>
<td>41 (20)</td>
<td>NS³</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>45 (24)</td>
<td>39 (19)</td>
<td>NS³</td>
</tr>
<tr>
<td>Irritability</td>
<td>75 (40)</td>
<td>53 (26)</td>
<td>0.018¹</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>74 (39)</td>
<td>51 (25)</td>
<td>0.019¹</td>
</tr>
</tbody>
</table>

NS: Not significant ¹ T-test (two-tailed) ² Chi-square test

There were no significant differences in handedness: in the migraine group 70% were righthanded (vs. 84% in the no-migraine group), 9% were left-handed (vs. 8%) and 21% had mixed handedness (vs. 8%).

Discussion

The present findings indicate that the major affective disorders associated with migraine are mostly unipolar depressive disorder and bipolar II disorder. Few of the migraine patients had bipolar I disorder. In addition it is noteworthy that almost half of the patients (45%) had an affective temperament. This constellation was significantly different from that seen in patients without migraine. The patients with migraine furthermore had an increased number of co-morbid anxiety disorders, especially panic disorder and agoraphobia. Other characteristics such as gender distribution, age, age at onset of major affective episodes, number of depressive episodes, marital status and frequency of alcohol or substance abuse did not differ significantly.

The symptoms of the depressive episodes were similar to those of patients without migraine, with equal frequencies of melancholic, atypical and psychotic symptoms. The only differences that emerged were increased frequencies of irritability and suspiciousness during depressive episodes among the patients with migraine. However, definite psychotic symptoms, both mood congruent and incongruent, were not more frequent among the migraine patients. One previous study on the personality of migraine sufferers found higher scores among women on the psychoticism scale of the Eysenck Personality Questionnaire (Brandt et al 1990), but other studies have been negative and have only reported increased levels of neuroticism (Merikangas 1994). Irritability may be both a part of the prodrome that often precedes migraine headaches (Davidoff 1995) and a prominent symptom during hypomanic/manic or mixed affective episodes. The increased frequency of irritability among the migraine patients in the present study may possibly reflect a linkage to bipolar disorders.

Mahmood et al (1999) have suggested that bipolar disorder associated with migraine might represent a more severe variant of bipolar disorder, based on an earlier onset of the bipolar disorder and greater social impairment. The present data do not indicate that patients with major affective disorders and migraine have a more serious affective disorder than patients without migraine. Age at onset of major affective episodes and the number of previous episodes were quite similar in the two groups.

Breslau et al (1994) found in an epidemiological study performed in Detroit that in persons having migraine (n = 128) the lifetime pre-
valence of major depression was 26.6% and dys-thymia 9.4%, compared to a prevalence of 4.7% for manic episodes and 3.9% for bipolar II disorder. This relationship between unipolar and bipolar disorders is clearly in contrast to the findings of the present study. One possible explanation for this difference may be selection bias in the present sample. The present definition of bipolar II disorder is also broader than the DSM-IV criteria. However, with regard to the difficulty of diagnosing hypomania it is not unlikely that a diagnostic assessment of a community sample in line with the present investigation would have yielded a higher frequency of bipolar II disorders (Akiskal 1996). In an epidemiological study performed in Zurich (Merikangas et al 1990), people with migraine (n = 61) had a threefold higher prevalence of mania or hypomania (8.8%) and a twofold higher prevalence of major depression (14.7%). These results are in accordance with our findings. Similarly, among patients attending a headache clinic, the lifetime prevalence of bipolar spectrum disorders was found to be 8.6% (Robbins and Ludmer 2000). In a study of patients from a private psychiatric practice (Endicott 1989), the highest frequency of migraine (51%) was found in patients with characteristics similar to bipolar II patients as defined in the present study. Patients with bipolar I disorder in that study had a migraine frequency of 22% and strictly unipolar depressive patients a frequency of 27%.

Both suicidal ideation and suicide attempts have been reported to be increased in patients with migraine with aura and major depression compared to patients with major depression without migraine (Breslau 1992). In the present study the number of patients with suicide attempts did not differ significantly between the groups with and without migraine. The most probable explanation is the high baseline frequency of suicide attempts in the whole sample, obscuring any preferential association with migraine.

The present findings are similar to those in other studies with regard to the association between migraine and anxiety disorders (Marazziti et al 1999; Marazziti et al 1995). Patients with migraine and major depression most often have a comorbid anxiety disorder (Merikangas and Stevens 1997), and this was also evident among the migraine patients in this study. Breslau and Davis (1992) found in a community study a doubled frequency of anxiety disorders among migraine patients, and the association was especially strong for panic disorder, with a sixfold increase. The temporal association between the onset of the different anxiety disorders, migraine and major depression is also similar to previous findings (Merikangas and Stevens 1997). There seems to be a constellation with an early onset of an anxiety disorder, most often a specific phobia (14.5 years in the present study), followed by migraine (21 years) and major depression (26.5 years).

The results both from this and from our previous, smaller study (Fasmer Submitted) indicate that there may be a preferential association between migraine and bipolar II disorder. There is substantial evidence that bipolar I and bipolar II disorders represent two different nosological conditions (Coryell 1996). It is, however, not always easy to separate hypomania from mania, and patients with unipolar depressive disorder may on closer scrutiny show signs of bipolarity or develop mania or hypomania during follow-up (Akiskal 1996). We therefore suggest that major affective disorders combined with migraine might represent a separate and distinct symptom cluster. As a group these patients may not simply be classified as belonging to either a unipolar or a bipolar disorder, at least not as defined according to DSM-IV. The present classification systems in psychiatry group patients with affective disorders into diagnostic categories on the basis of characteristic constellations of affective symptoms. However, it seems reasonable to envisage that different pathophysiological mechanisms may cause similar constellations of clinical psychiatric symptoms.

At the present stage of our knowledge, significant comorbid patterns may be the most promising way of creating new and more useful classification schemes. This has been suggested with regard to panic disorder in patients with bipolar disorder (MacKinnon et al 1998). The use of a non-psychiatric disorder such as migraine may perhaps also be employed to define subgroups among the affective disorders.

Migraine is an organic disorder with a genetic background, although environmental factors are also important both aetologically and in the precipitation of individual attacks (Davidoff 1995). Vascular symptoms are prominent, but it is now fairly well established that the primary pathophysiological disturbance is neuronal (Davidoff 1995). Apart from the association of migraine with defined anxiety and affective disorders it is also well known that prodromal and accompanying symptoms of migraine attacks are often psychiatric in nature, such as depression, elation, irritability and anxiety (Davidoff 1995).

Neuropsychological investigations into migraine have produced substantial information concerning the pathophysiology of this disorder (Hargreaves and Shepheard 1999). It does not seem unreasonable to suppose that there must be a basic neuropsychological derangement responsible both for the short-lasting, episodic phenomena seen in these patients (migraine, panic attacks, hypomania) and for the longer-lasting disturbances (major depression, affective temperaments). This may possibly be linked to disturbances in either the serotonergic (Wang et al 1996; Chugani et al 1999) or the dopaminergic system (Peroutka 1997).
With regard to disturbance of 5-HT neurotransmission, van Praag (1994) has suggested that altered 5-HT neurotransmission is central to the pathophysiology of affective disorders, and that there is a subtype of depression characterized by 5-HT disturbance accompanied by anxiety and/or aggression. The increased number of anxiety disorders and prominent irritability as found in the present study among patients with major affective disorders and comorbid migraine suggest that migraine could well be fitted into such a pattern. We also found a significantly increased frequency of anorexia among the migraine patients in this study (17% compared to 4% in the no-migraine patients), and there is evidence for disturbances in 5-HT neurotransmission in patients with eating disorders (Kaye 1991). Other links may be the increased frequency of suicidal thoughts and suicide attempts found among patients with migraine (Breslau 1992), and the high frequency of migraine among patients with impulse-control disorders (McElroy et al 1998).

We found a high frequency of asthma (30%) among the migraine patients in this study. This was not surprising, since there is a well-known association between asthma and migraine (Chen and Leviton 1990). However, we did not find any association between migraine and Raynaud's syndrome. There were no significant differences in handedness between the two groups. Although it was once claimed that there is an increased frequency of left-handedness among migraine patients, this was refuted in subsequent studies (Messinger et al 1988).

The major limitation of the present study is the difficulty of knowing whether the results may be generalised to patients with major affective disorders in the general population. The patients who were interviewed in this study clearly represented a selected group. However, the findings probably give an indication concerning the frequency of migraine in patients attending psychiatric hospitals and underscore the importance of including questions on migraine when taking the history of these patients. Relatives were not systematically interviewed. If this had been done it might have given a better separation of bipolar II disorder from unipolar depressive disorder, and this could perhaps also have allowed a better delineation of the affective temperaments. Concerning the statistics we have chosen to present P-values without trying to correct for multiple comparisons. With regard to the characteristics of depressive episodes the most noteworthy is probably the lack of significant differences, and the findings of increased irritability and suspiciousness will require confirmation in a larger sample. Concerning the affective subtypes and temperaments on the other hand, the results seem robust and it is probably more important to see if these findings can be confirmed in a community sample.

It would have been interesting to examine patients with migraine without aura and migraine with aura separately, but this would require a larger number of patients. Results from epidemiological studies indicate that migraine with aura may have a stronger association with psychiatric disorders than migraine without aura (Breslau et al 1994). This is in agreement with our finding that a larger number of patients have migraine with aura than migraine without aura, but it is in contrast to the findings of Endicott (1989), who reported a larger number of patients with "common" compared to "classical" migraine among patients with major affective disorders. Similarly it would be interesting to look for biological differences between the two groups of unipolar depressive patients, those with and those without migraine. If the hypothesis presented in this paper is correct, i.e. that the presence of migraine separates a distinct subgroup of affective disorders, there ought to be differences between these groups, perhaps most likely in measures reflecting altered serotonergic or dopaminergic neurotransmission.

Acknowledgements

We would like to thank Per Bergsholm M.D. for helpful discussions concerning the diagnosis of affective temperaments.

References


Chugani DC, Niimura K, Chaturvedi S, Muzik O, Fakhouri M, Lee ML, Chugani HT (1999) Increased brain serotonin synthesis in...


Fasmer OB (Submitted) Migraine and bipolar II disorder. Cephalalgia.


Hans-Jürgen Möller
Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany

Summary
These excerpts from the Presidential Address at the 7th World Congress of Biological Psychiatry, Berlin, 2001 attempt to define the term "biological psychiatry", the principle relevance of diagnostic systems for biological psychiatry and the relevance of biological psychiatry in the past and future for the development of psychiatry in general. They also cover the problem of misuse of biological psychiatry and the need for the rigorous observation of ethical standards.

Key words: biological psychiatry, methodology of biological psychiatry, psychiatric classification.

Correspondence:
Prof. Hans-Jürgen Möller
Department of Psychiatry
Ludwig-Maximilians-University
Nussbaumstr. 7
80336 Munich
Germany
Tel: +49 89 5160 5501
Fax: +49 89 5160 5522
E-mail: hans-juergen.moeller@psy.med.uni-muenchen.de

Excerpts from the Presidential Address at the 7th World Congress of Biological Psychiatry, Berlin, 1st July 2001

Psychiatric disorders play an enormous role in terms of both their prevalence and their individual and social consequences, including the health-economic consequences. All of these are good reasons for politicians to demonstrate their commitment to this field and to ensure that, based on increasing research activities, the diagnosis and treatment of these diseases can be improved. Most politicians have understood that neuroscience and psychopharmacology are, among and together with other approaches, particularly important tools to achieve the goal of treating severe psychiatric diseases such as depression, schizophrenia, Alzheimer's dementia and others, and to improve the quality of life of the patients suffering from such diseases.

German psychiatry has a very recognised scientific tradition. In this context I would like to mention only a very few names, such as Griesinger, Kraepelin, Alzheimer, Bonhöfer, Jaspers and Schneider. From an international perspective, Kraepelin and Alzheimer are especially well known and can be seen as the fathers of biological psychiatry. This historical background was also considered when it was decided that the 7th World Congress of Biological Psychiatry should take place in Germany. Of course, the major aim of this congress is not to look back in a historical fashion, but to look at the present and into the future. Particularly the latter aspect led to the subtitle for this congress: "Gateway to biological psychiatry in the new millennium". Although we will focus on the current situation and the future perspectives, it is often meaningful to include the retrospective viewpoint to understand better what is going on.

I particularly thought of this when in 1998, in my position as Chairman of the Department of Psychiatry of the University of Munich, where Kraepelin and Alzheimer used to work at the beginning of the 20th century, we opened the renovated historical building of our department, which was originally built under the guidance of Kraepelin. When Kraepelin opened this building in 1904, there was almost no effective biological treatment in psychiatry available, besides some sedative drugs. The lack of effective treatment procedures at that time is reflected by the excessive use of the so-called "bath therapy". The historical building of our department, the
Kraepelin building, was especially designed in a way to facilitate this bath therapy in a differentiated way. If we compare 1904 with the current situation, almost 100 years later: what a difference! Kraepelin, together with others, created the basis for an empirical classification and a biological understanding of psychiatric diseases, which later led to the development of effective biological treatments. It is sometimes necessary to look back into history to better recognise the great progress of psychiatry and, of course, also to analyse how this progress was achieved.

We all agree that the achievements of biological psychiatry in the past 100 years were enormous, starting with the scientific work of Kraepelin and Alzheimer at the beginning of the 20th century, through the development of the modern psychopharmacological treatments, and related chemical hypotheses of depression, schizophrenia and anxiety disorders in the middle of the 20th century, and leading to the modern aetiopathogenetic understanding of psychiatric diseases based on molecular genetics, brain imaging etc., at the end of the 20th century.

If we try to extrapolate from this historical perspective to the first century of the new millennium, we really run into futuristic ideas of a possible new classification of psychiatric diseases, which could be based to a great extent on causal explanations related to molecular genetics and other biological findings, and on a much more specific, cause-related pharmacotherapeutic approach as well as possibly on other biological treatment strategies. It is of greatest importance that biological psychiatry proceeds in this direction in future, to guarantee as far as possible a better understanding and a more effective treatment of psychiatric diseases. Keeping this in mind we are forced to further develop biological psychiatry all over the world and to improve treatment for psychiatric patients to the optimum.

Of course, biological psychiatry is only one part of psychiatry, possibly the most important one from the perspective of research-oriented biological psychiatrists, but we have to consider that psychiatry in general also includes other specialities and research fields like social psychiatry and psychotherapy. There is no doubt that when we, as doctors, treat our patients, these aspects have to be integrated and we have to combine the perspective of biological psychiatry with the psychosocial aspects of psychiatry. Biological psychiatry is only one part of general psychiatry, but a very important one which has already achieved a lot and which promises much further progress.

What is the meaning of the term "biological psychiatry"? It is not so easy to explain this term in the full meaning of its content. This term may not be the best, but it has grown historically and it has its tradition. The easiest way to explain it, especially if we only have a research focus, is to define it as applied neuroscience in the field of psychiatric disorders. But many clinicians, defining themselves primarily as biological psychiatrists, have the feeling that this definition is too narrow. They say that biological psychiatry is more than just the application of neuroscience to psychopathological phenomena and that clinical psychiatry itself also has characteristics typical of biological psychiatry, including good observation, description and classification of the clinical phenomena.

This leads to the following question: What are the basic characteristics of clinical biological psychiatry and, of course, what are the characteristics of biological psychiatry as a whole? If we do not only want to recur to the more-or-less tautological definition that biological psychiatry sees psychiatric and psychological phenomena in the context of biological theory, we could focus on another, more methodological characteristic, namely the empirical approach. And if we look back at the history of the origins of the term and discipline "biological psychiatry", we can detect that it was established about 30 to 40 years ago, when a very ideological social psychiatry/antipsychiatry was trying to convince people, based on more-or-less completely unproven hypotheses, that psychiatric diseases are, for example, only caused by psychosocial factors, or that they do not really exist and/or are only the consequence of a labelling process. At that time the necessity of an adequate empirical approach, to avoid such ideologically based misinterpretations, was recognised. If we define biological psychiatry by empirical methodology, then we could say that not only biological but also psychosocial parameters are a focus of biological psychiatry, as long as an empirical methodology is followed.

From a clinical point of view, classical descriptive psychopathology is often seen as the centre of empirical psychiatry. But it could be questioned whether classical descriptive psychopathology, with all its subtleties, really can advance the outcome of research in biological psychiatry. The traditional psychiatric classification, as well as its modern version, the operationalized classification systems, have been especially criticised, mainly by arguing that most diagnostic categories do not merely represent diseases but complex syndromes consisting of certain psychopathological features together with some course characteristics, and they are in opposition to a disease model not related to a specific aetio-pathogenesis. To take an alternative position, we could be faced with the hypothesis that these complex syndromes are not associated in a very direct way with the neurobiological background, a position that was already published by Karl Bonhöfer in his concept of exogenous psychosis
at the beginning of the 20th century. Based on these reflections, over the last decades there have also been tendencies in biological psychiatry to omit the traditional clinical classification and only to look for certain types of elementary behavioural categories, like van Praag did in his functional psychopathology. Another position, driven by the more basic research-oriented colleagues, was the idea that it might be much more meaningful to establish a classification that is principally based on biological parameters and not on parameters of clinical psychopathology. However, the latter approach was apparently hitherto unsuccessful, or at least not accepted either for research or for clinical purposes. On the other side, the fascinating development of genomics again led some researchers to hope that a genomic-based descriptive classification could be achieved as the best way for the future of biological psychiatry.

Biological psychiatry is often viewed critically, sometimes extremely critically, by several groups. We have to understand the reasons for this in order to be able to deal with it in an adequate way. The reasons vary: they range from principle criticism of biologically-oriented research in volunteers or in psychiatric patients, through criticism of biological therapies like psychopharmacotherapy and fears concerning misuse of biological psychiatry, particularly the misuse of genetics, to historical reflections about the misuse of psychiatry under different political systems and conditions.

This gives the link to the very problematic part of German psychiatry and history in the time of the Nazi regime. The horrible and completely inhuman misuse of psychiatry, as occurred in the euthanasia and holocaust scenario, is difficult to understand, but it gives biological psychiatry in general and especially German psychiatrists a special necessity to observe extremely attentively ethical standards of psychiatric research and psychiatric care.
Acne, Isotretinoin Treatment and Acute Depression

Chee Hong Ng1, Mei Mui Tam2, Stephen J Hook
1 Department of Psychiatry, University of Melbourne, Australia
2 Department of Dermatology, St Vincent’s Hospital (Melbourne), Australia

Summary
The association between isotretinoin therapy and depressive symptoms in acne patients has generated much recent interest but has not been systematically explored.

A 17-year-old man with acne vulgaris developed symptoms of acute depression two weeks after beginning isotretinoin therapy. The depressive symptoms improved with reduction of isotretinoin dose and treatment with sertraline. Of note, however, is that when the isotretinoin dose was again increased, the depressive symptoms recurred despite clearing of the skin, leading to an unsuccessful suicide attempt. Isotretinoin was finally discontinued and the depression rapidly resolved. Although the effects of hypervitaminosis A may be involved aetiologically, the predictive factors of drug-related depression remain unclear. Significant depressive symptoms that develop during the course of treatment need close monitoring and may necessitate both antidepressant therapy and discontinuation of the drug. Given the uncertain causal relationship between isotretinoin and depression, versus the potential psychological benefits of effective acne treatment, systematic studies exploring the impact of isotretinoin on mood are needed.

Key words: acne, isotretinoin, depression, suicide, causal relationship.

Correspondence:
Dr. Chee Hong Ng
Department of Psychiatry
University of Melbourne
Professorial Unit, The Melbourne Clinic
130 Church Street
Richmond
Victoria
Australia 3121
Tel: +61 3 9420 9350
Fax: +61 3 9428 5990
E-mail: ngc@svhm.org.au

Introduction
Acne is a common condition affecting young patients. A significant proportion of those with moderate to severe acne is treated with systemic isotretinoin, particularly if there are concerns about facial and bodily appearance. Isotretinoin, a vitamin A derivative (13-cis-retinoic acid), is a highly effective treatment for cystic acne. While side effects like dry skin, photosensitivity, lethargy and abnormal liver and lipid functions are well known (Wolverton 1991), its effect on mood is less well documented. Severe depression can develop for the first time following isotretinoin use in a subgroup of patients, as is highlighted by the following case.

Concern about depression associated with isotretinoin use from numerous reports has led to much recent publicity linking the risk of depression and other psychiatric effects with isotretinoin. The Adverse Drug Reactions Advisory Committee has received at least 12 reports since 1986 of depression related to isotretinoin in Australia (ADRAC 1998). Furthermore, the U.S. Food and Drug Administration has reported about 24 cases where depression resolved when therapy was ceased but recurred when treatment was reintroduced (Ault 1998). Consequently, product information was recently changed, warning that isotretinoin may cause depression, psychosis, and rarely suicidal ideation, suicide attempts and suicide.

Recently, a retrospective cohort study of 7535 isotretinoin users from two large population health databases found no increase in relative risk estimates for depression, psychotic symptoms, suicide and attempted suicide (Jick et al 2000). Despite having the largest data set yet published, the study remains inconclusive because of methodological limitations including the retrospective study design, use of a computerised database, inadequate method used for case recognition and lack of psychometric measures. Significant variables like severity of acne, treatment compliance, concomitant medications and comorbid conditions were not adequately controlled. It is also possible that anecdotal case reports may be picking up a small subgroup of patients at risk of developing depression but too few to show significant differences in systematic studies.

Case report
We report the case of a 17-year-old male who
developed acute depression and suicidal ideation during a course of treatment with isotretinoin for moderately severe facial acne vulgaris. The patient was previously a well-adjusted and active adolescent although he had been self-conscious about the facial acne he suffered for the last five years. He had no premorbid history of any psychiatric problems but there was a family history of post-natal depression. Despite previous topical treatment with adapalene 0.1% gel and azelaic acid 5% cream, and 18 months therapy with antibiotics (doxycycline hydrochloride), he still had moderate inflammatory acne consisting of multiple papules, pustules and comedones. After discontinuing the topical therapy and antibiotics he was immediately commenced on isotretinoin (0.63 mg/kg/day) for the first time following normal routine physical and laboratory examination. About two weeks into treatment he began to develop depressive symptoms over several weeks which included irritability, insomnia, decreased appetite, lack of motivation and interest, social withdrawal and suicidal ideation. Subsequently, his family reported that after the onset of depression, he had angry outbursts related to alcohol use that had not previously occurred. He also stopped his regular attendance to both school and the gym.

His isotretinoin dose was reduced (0.32 mg/kg/day) for two weeks and he was commenced on sertraline 50 mg, which was gradually increased to 150 mg. He responded to sertraline and his symptoms further improved with the support of his general practitioner and a counsellor. However, he also had high expectations of the anti-acne drug and became disappointed when the skin dryness he experienced (a side effect of isotretinoin) had temporarily worsened his facial appearance. As his self-consciousness about his skin may have been aggravating his depression, the higher isotretinoin dosage was resumed to treat his acne and help alleviate any negative psychological impact. After another two weeks, the patient further increased the dose of isotretinoin (1.0 mg/kg/day) to achieve a more rapid and effective response.

However, three months into treatment his mood deteriorated and the depressive symptoms relapsed, despite significant improvement of his skin status and being compliant with sertraline. He was not enjoying his casual work and he felt increasingly frustrated and hopeless. Consequently, he planned and attempted suicide by ingesting a substantial overdose of pseudoephedrine and diazepam, medications that belonged to his parents. Fortunately his family found him and he was treated at the local emergency department.

Following discharge to the care of his general practitioner, he was referred to a consultant psychiatrist who confirmed the diagnosis of severe major depressive disorder associated with isotretinoin treatment (Hamilton Depression 17-item scale score of 28). The patient was maintained on sertraline at 150 mg but isotretinoin was ceased. Altogether he had taken 7200mg (114mg/kg) of isotretinoin. At the time of discontinuation of isotretinoin, his skin was clear and it did not worsen subsequently. Over the next two weeks his mood, sleep, appetite, energy levels and motivation improved rapidly and he was no longer suicidal. After six weeks, he reported no depressive symptoms and had returned to normal functioning, working full time and attending the gym regularly.

Discussion

Data from the current literature on the possible association between isotretinoin and depression is mostly limited to brief anecdotal case reports published in non-psychiatric journals (Scheinman et al 1990; Gatti and Serri 1991; Peck et al 1991; Bravard et al 1993; Hazen et al 1983). One study reported spontaneous depression in 1% out of 700 patients participating in a clinical trial with isotretinoin, which was unrelated to dosage (range of 0.3 to 1.3 mg/kg/day) or period of exposure (Scheinman et al 1990). The depressive symptoms resolved rapidly within two to seven days after cessation of isotretinoin. The authors suggested that depression is a rare idiosyncratic adverse effect that may develop during isotretinoin therapy in predisposed patients. Another report raised concern about the severity of such drug-induced depressive illness particularly affecting younger patients, quoting cases of reported suicides involving mainly patients aged under 18 (Byrne and Hnatko 1995). Anecdotal studies also suggest that total discontinuation of the drug may be a necessary condition for sustained recovery from depression (Ault 1998; Bravard et al 1993; Scheinman et al 1990). Crying spells, irritability, malaise and headache can be produced by benign intracranial hypertension related to hypervitaminosis A associated with treatment with retinoids (Scheinman et al 1990; Byrne and Hnatko 1995). The similarities to these neuropsychiatric symptoms and the drug challenge/rechallenge data implicate possible mechanisms involved in isotretinoin-induced depression.

Clinicians should assess the risk factors and past history of depression prior to prescribing isotretinoin, although the predictive factors of drug-related major depression remain uncertain. Any depressive symptoms that develop during the course of treatment need close monitoring and may require prompt psychiatric assessment. Significant depression may necessitate both discontinuation of the drug and further evaluation for antidepressant therapy. Resolution of depression associated with isotretinoin appears to be rapid and complete with appropriate treatment.
On the other hand, severe acne, especially in adolescents and young adults, is frequently associated with depression, anxiety, low self-esteem, body image problems, self-consciousness, lack of self-confidence, social withdrawal and psychological distress (Gupta and Gupta 1998; Koo 1995). Hence effective acne treatment is likely to result in a positive psychological outcome (Kellett and Gawkrodger 1999; Rubinow 1987; Macdonald Hull et al 1991) and better quality of life. However, in the above case, the depression worsened despite clearing of the acne. Another aspect relates to possible unrealistic expectations following treatment that the clearing of the disfiguring skin condition would lead to resolution of personal and social inadequacies (Gatti and Serri 1991; Peck et al 1991). Such unfulfilled hopes may heighten the sense of failure previously attributed to the acne and precipitate depression.

Given the uncertain causal relationship between isotretinoin and depression, versus the potential psychological benefits of effective acne treatment, carefully designed systematic studies exploring the impact of isotretinoin on mood are needed. A prospective study comparing the effect on depressive symptoms and quality of life in patients treated with isotretinoin versus those treated with antibiotic or topical therapies is currently being conducted to further clarify these issues (Ng et al: unpublished data).

References