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Editorial

Neurotransmitters, Neurosteroids and Neurotrophins: New Models of the Pathophysiology and Treatment of Depression

A common notion underlying our understanding of major depression and leading to the development of antidepressant drugs is that a functional decrement in central nervous system (CNS) monoamine activity is a key alteration and that antidepressants must increase intra-synaptic monoamine concentrations to be effective. Indeed, the so-called "biogenic amine" or "monoamine" hypothesis of affective disorders was derived by extrapolating from the presumed mechanism of action of drugs that treated or provoked affective symptoms (Schildkraut and Kety 1967). In turn (and in what may have been an unfortunate example of circular reasoning), antidepressant drug development has primarily focused on enhancing, or making more selective, such actions on monoamines. In this Editorial, we propose that diminished CNS monoamine activity represents one route to developing major depression (Charney 1998), but not the only one. Similarly, we propose that monoamine-enhancing actions are one route to successful antidepressant action but not the only one. To the extent these possibilities are true, clarifying alternative biological abnormalities in major depression and/or identifying biologically distinct subgroups of patients should permit more effective and rational pharmacotherapy.

Limbic-hypothalamic-pituitary-adrenal axis: CRH and cortisol

The most well-replicated biological abnormality in major depression is hyperactivity of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, and normalization of LHPA axis activity may be a prerequisite for stable remission in hypercortisolemic depressives (reviewed in: Murphy 1991). Traditionally considered a reflection of stress or of CNS neurotransmitter changes which, themselves, were more closely related to the aetiology of depression, the LHPA axis changes in major depression are now being seen as directly contributing to the pathogenesis of the depressed state, at least in some patients (Murphy 1991; Reus and Wolkowitz 2001; Wolkowitz et al. 2001; Wolkowitz and Reus 1999). Multiple mechanisms exist at different levels of the LHPA axis whereby LHPA over-activity may initiate, perpetuate or alter the presentation of major depression. For example, centrally-active corticotrophin-releasing hormone (CRH) may be directly anxiogenic and depressogenic, causing (in animals injected intracerebroventricularly with CRH) fearfulness, disturbed sleep, diminished reproductive activity and diminished food intake (Dunn and Berridge 1990). Increased production of CRH may be a primary deficit in depression or may be secondary to an alteration in corticosteroid signalling (Holsboer 2000). Prolonged elevations in cortisol levels may also contribute to depression: cortisol, via classic genomic mechanisms, alters the transcription and synthesis of proteins pivotal to monoamine homeostasis. For example, over-exposure to corticosteroids may promote serotonin system down-regulation, whereas anti-glucocorticoid treatment may have antidepressant effects via increases in serotonin sensitivity (reviewed in: Reus and Wolkowitz 2001; Wolkowitz et al. 2001). Over-exposure to glucocorticoids may also prove neuroendangering or neurotoxic to the brain (Sapolsky 2000). These effects are, in part, secondary to excitotoxic nerve damage and decreased release of neurotrophic factors, mechanisms that may point to novel antidepressant strategies, as discussed below. The neuroendangering/neurotoxic potential of glucocorticoid over-exposure has been conclusively demonstrated in several animals species, and suggestive evidence in support of this exists in humans (McEwen and Magarinos 2001; Sapolsky 2000). Patients with Cushing's disease, for example, demonstrate diminished hippocampal volume, which at least partially resolves upon correction of the hypercortisolaemia (Starkman et al. 1999). Patients with major depression also exhibit decreased hippocampal volume, proportionate to their lifetime days of depression (Sheline et al. 1999), but it is unknown whether this is related to cumulative exposure to cortisol and whether antidepressant treatment abrogates the volume loss. Antidepressant medications, regardless of chemical class or nominal mechanism of action, up-regulate brain glucocorticoid receptors (Barden et al. 1995; Holsboer 2000). Such effects may represent a novel and pivotal common mechanism of action of antidepressants, since up-regulation of glucocorticoid receptors enhances the LHPA axis's ability to recognize and appropriately respond to elevated glucocorticoid levels (i.e., it sensitizes and normalizes negative feedback responsivity) (Barden et al. 1995). Consequently, inappropriate CRH release is curtailed (theoretically producing antidepressant or anti-anxiety effects), and cortisol levels are normalized (theoretically restraining abnormal genomic regulation and protein synthesis, diminishing cortisol's negative effect on serotonin system activity, and preventing further hippocampal damage). In support of such a mechanism of action of antidepressant drugs, drugs that curtail glucocorticoid activity but that have no direct effects on monoamines (e.g., glucocorticoid biosynthesis inhibitors (Reus and Wolkowitz 2001; Wolkowitz and Reus 1999), steroid receptor blockers (Belanoff et al. 2002) and CRH-1 receptor

antagonists (Holsboer 1999)) have shown preliminary evidence of antidepressant efficacy in some patients. In the future, interventions that directly target the corticosteroid receptor and CRH genes may prove to be even more selective and effective means of therapeutic intervention (Muller et al. 2002).

Neurosteroids

Although cortisol is the most widely studied steroid in depression, numerous other adrenal steroids are biologically active in man (Murphy 1991). Further, a recently identified class of steroid hormones – "neurosteroids"— exists that is synthesized *in situ* in brain, has rapid (non-genomic) effects at classical neurotransmitter receptors and has potent behavioural activity (Rupprecht 2003; Rupprecht and Holsboer 1999). Although the study of such steroids and neurosteroids in major depression is in its infancy, interesting and suggestive leads are accumulating. Dehydroepiandrosterone (DHEA), together with its sulphated metabolite DHEA-S, is interesting to consider for several reasons (reviewed in Wolkowitz and Reus 2000): (1) DHEA(S) levels markedly decrease with age in both men and women, (2) DHEA(S) levels increase in response to acute stress, in parallel with cortisol, but markedly decline with chronic stress and with chronic illness, even though cortisol levels may remain elevated, (3) DHEA(S) appears to exert significant anti-glucocorticoid activity, perhaps serving to constrain acute stress responses and to offset deleterious effects of hypercortisolaemia. For example, in pre-clinical models, DHEA(S) prevents glucocorticoid and excitotoxicity-induced hippocampal damage. (4) Cross-sectional and longitudinal studies have noted relatively higher DHEA(S) levels (or higher DHEA(S)/cortisol ratios) in individuals who are physically and mentally healthier or who exhibit greater longevity, but these findings have not been uniformly replicated. Patients with major depression have been found to have low, high or unaltered levels of DHEA(S), compared to matched controls, and the reasons for these discrepancies are not yet apparent. Nonetheless, emerging double-blind, placebo-controlled trials suggest that DHEA has significant antidepressant effects in patients with major depression (Wolkowitz et al. 1999), midlife-onset dysthymia (Bloch et al. 1999), and schizophrenia (Strous et al. 2003).

Another neurosteroid under active investigation is 3α, 5α-tetrahydroprogesterone (allopregnanolone). Allopregnanolone is a potent endogenous agonist of the GABA-A receptor, and it may play a role in endogenous stress relief and in multiple neuropsychiatric conditions (Rupprecht 2003; Rupprecht and Holsboer 1999). In addition to non-genomic (cell surface receptor-mediated) effects, allopregnanolone and certain other neurosteroids can enter the cell, where they are oxidized to substances that bind cytosolic progesterone receptors, leading to genomically-mediated effects, such as alterations in GABA-A receptor subunit composition, decreased expression of genes coding for CRH and increased expression of genes coding for proteins involved in myelin repair (reviewed in: Rupprecht 2003; van Broekhoven and Verkes 2003). Untreated patients with major depression have low plasma (Romeo et al. 1998; Strohle et al. 1999) and CSF (Uzunova et al. 1998) levels of allopregnanolone, and allopregnanolone levels increase in response to antidepressant treatment (Romeo et al. 1998; Strohle et al. 1999; Uzunova et al. 1998); these increases parallel clinical improvement in depressed patients (Uzunova et al. 1998). One mechanism by which certain antidepressants increase allopregnanolone levels is increasing the oxidative efficiency of 3α-hydroxy-steroid dehydrogenase (HSD), the enzyme that converts dihydroprogesterone to allopregnanolone (Griffin and Mellon 1999). This effect may represent an important and novel mechanism underlying the antidepressant and anti-dysphoric effects of SSRI antidepressants (Guidotti and Costa 1998). Other neurosteroids that may be involved in the pathogenesis of depression and anxiety disorders and in the therapeutic effects of antidepressants (e.g., 3α, 5α-tetrahydrodeoxycorticosterone [THDOC] [a GABA-A receptor agonist] and 3β, 5α-tetrahydroprogesterone as well as pregnenolone and pregnenolone sulfate [GABA-A receptor antagonists]) are beginning to be studied (Meieran et al. In Press; Rupprecht 2003; Strohle et al. 2003; Strohle et al. 1999; van Broekhoven and Verkes 2003).

Neurotrophins

Perhaps the most revolutionary and exciting new theory of depression and of antidepressant drug action was promulgated by Duman and colleagues (Duman et al. 1997). In this model, based on pre-clinical data, stress (as well as increased glucocorticoid hormone levels and decreased serotonin and norepinephrine levels) can lead to altered intra-neuronal second messenger signalling, culminating in a diminution of brain trophic factors, such as brain-derived neurotrophic factor (BDNF). Such

effects could inhibit ongoing neurogenesis in the hippocampus (and to a lesser extent the prefrontal cortex) and could conceivably contribute to the hippocampal volume losses seen in some depressed patients and in patients with Cushing's disease, described above. Loss of hippocampal neuronal cells might provoke certain cognitive and emotional symptoms of major depression (Reid and Stewart 2001), although a direct role of hippocampal dysfunction in major depression remains to be demonstrated. According to Duman and colleagues' hypothesis, antidepressant-induced increases in hippocampal BDNF levels can blunt the ability of chronic stressors (or glucocorticoid excess) to damage vulnerable neurons (Duman et al. 1997). Interestingly, direct infusion of BDNF into rat brain has antidepressant-like effects (Siuciak et al. 1996), and chronic treatment with all known classes of antidepressant medications (e.g., tricyclics, SSRI's, MAO-I's, lithium) significantly increases hippopcampal BDNF expression in rats. These increases parallel the time course of clinical response to such antidepressant drugs in depressed patients. Emerging human data support the relevance of BDNF for clinical depression. Depressed patients have low serum levels of BDNF, and BDNF levels are inversely correlated with the severity of depressive symptoms (Karege et al. 2002; Shimizu et al. In Press); the relationship of serum BDNF levels to brain BDNF levels, however, is unknown. Lastly, antidepressant-treated depressed patients, compared to untreated ones, have relatively higher hippocampal levels of BDNF at autopsy (Chen et al. 2001). Antidepressants, therefore, may normalize hippocampal levels of BDNF; this might lessen the hypothesized neurotoxic sequellae of depression.

Glutamate

Among the mechanisms by which stress and glucocorticoid excess can culminate in neuronal toxicity is excitotoxic injury, mediated by the NMDA receptor (Sapolsky 2000). Glutamate antagonists acting at the NMDA receptor protect vulnerable neurons against a variety of insults, including stress and glucocorticoid-induced damage; they are also capable of increasing BDNF synthesis and increasing neurogenesis in the dentate gyrus (reviewed in Skolnik 1999). Perhaps through these or other mechanisms, NMDA antagonists may represent another emerging class of antidepressant medication (reviewed in: Krystal et al. 2002; Skolnik 1999). Consistent with an antidepressant effect of NMDA receptor antagonism is the observation that chronic treatment with standard antidepressants alters NMDA receptor subunit composition and dampens regional NMDA receptor function (Skolnik 1999).

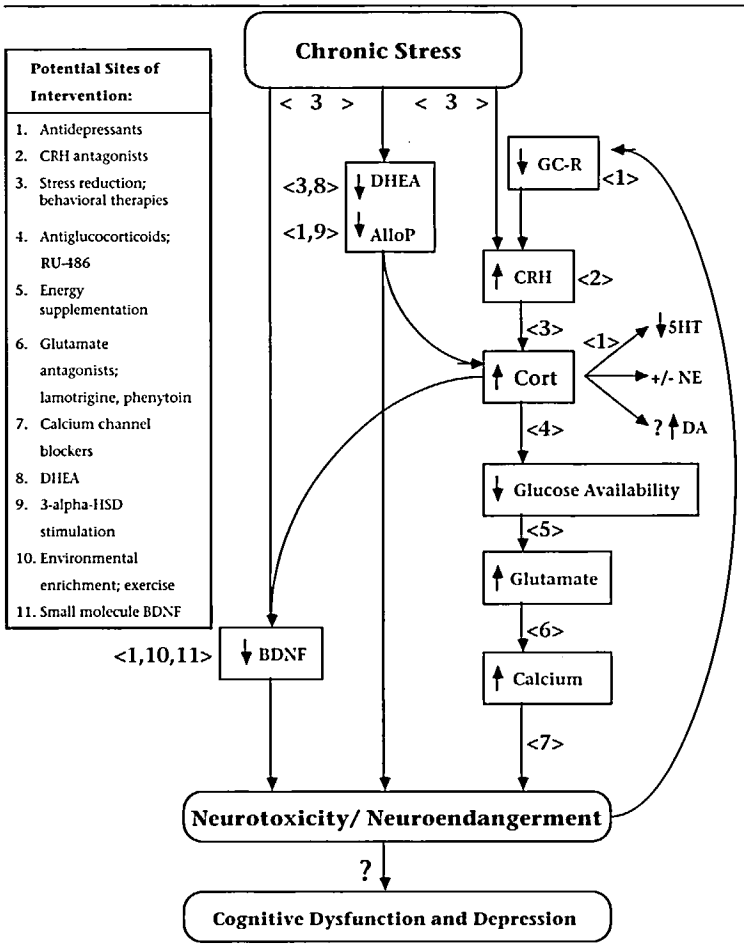
GABA

Multiple lines of evidence suggest an impairment in GABA activity in major depression (reviewed in Krystal et al. 2002). For example, magnetic resonance spectroscopic imaging has revealed decreased occipital cortical GABA concentrations in depressed patients. This abnormality, which co-occurs with increased glutamate concentrations in the same voxels, is seen in unipolar depressed patients, particularly those with psychotic or melancholic depressions, but is not seen in bipolar or atypical depressives (reviewed in Krystal et al. 2002). SSRI's, as well as ECT, eliminate the cortical GABA abnormality seen in depressed patients (Krystal et al. 2002). In addition, as mentioned above, SSRI's (and perhaps other antidepressants) increase brain levels of certain GABA-A receptor agonist neurosteroids, such as allopregnanolone, thereby further enhancing GABA-ergic activity. Lastly, fluoxetine, an SSRI, directly modulates activity of GABA receptors via interactions at a novel modulatory site, increasing GABA receptor response to sub-maximal concentrations of GABA (Robinson et al. 2003).

Table 1

Non-monoaminergic mechanisms of standard antidepressants

1. Increased glucocorticoid receptor binding (resulting in increased sensitivity of glucocorticoid receptors to negative feedback and in decreased CRH and cortisol levels)
2. Increased brain levels of allopregnanolone, a GABA-A receptor agonist neurosteroid (especially SSRI's?)
3. Increased cortical GABA levels (SSRI's and ECT); increased sensitivity of GABA-A receptors to sub-maximal concentrations of GABA (fluoxetine)
4. Increased BDNF levels (resulting in increased hippocampal neurogenesis and in lessened stress-induced decreases in hippocampal neurogenesis)
5. Altered NMDA receptor subunit composition and dampened regional NMDA receptor function



Several routes contributing to major depression are envisioned. These routes may develop independently or in tandem, but once developed, frequently interact with the other routes. Chronic stress, for example, (or as yet unidentified biological predispositions combined with environmental precipitants) sets in motion: (1) Increased LHPA axis activity. With prolonged or uncontrollable stress, glucocorticoid receptors (or glucocorticoid receptor-rich areas of the brain, such as the hippocampus) may downregulate, resulting in failure of negative homeostatic mechanisms and unrestrained hyperactivity of the LHPA axis. The resulting high levels of CRH may directly provoke depressive and anxious symptoms, while the high levels of cortisol may, via genomic mechanisms, alter monoamine activity in the direction of causing depressive, anxious or psychotic symptoms (e.g., decreasing serotonin responsivity and increasing dopamine activity). Chronically elevated cortisol levels may provoke hippocampal neurotoxicity or neuroendangerment, via intraneuronal glucoprivation, excess glutamate accumulation (culminating in excitotoxicity), increased release of calcium from intraneuronal stores and free radical liberation. Resulting hippocampal dysfunction may contribute to depressive symptoms, but this has not been clearly established. (2) Decreased DHEA(S) and GABA-ergic neurosteroid (e.g., allopregnanolone) activity. Loss of protective neurosteroids could limit the brain's ability to withstand hypercortisolemic or excitotoxic hippocampal damage, and diminution of GABA-ergic neurosteroid activity could facilitate the emergence of anxiety-like and dysphoric symptoms. (3) Decreased neurotrophin synthesis. Stress-induced loss of BDNF activity would limit ongoing hippocampal (and prefrontal cortical) neurogenesis and would curtail the brain's ability to recover from incident damage. Decreased BDNF activity could also indirectly contribute to depression via monoaminergic mechanisms, since BDNF exerts trophic effects on serotonergic and dopaminergic neurons (reviewed in: (Skolnik 1999)). Other pathways not diagrammed in this Figure include dysregulated NMDA receptor activity, GABA-A receptor activity, substance P activity, neuropeptide Y activity and neuroinflammatory modulators (e.g., cytokines), among others. Whereas monoaminergic antidepressant interventions have a clear treatment role in this model, other loci are highlighted as being amenable to intervention (e.g., CRH antagonism, glucocorticoid inhibition, intracellular energy supplementation, glutamate [NMDA] antagonism, calcium blockade, DHEA supplementation, GABA-ergic neurosteroid synthesis promotion [e.g., stimulation of 3-α-HSD], neurotrophin synthesis promotion, etc.).

Figure 1. Hypothetical interplay of stress-induced steroid, neurosteroid, neurotransmitter and neurotrophin dysregulation, culminating in neuroendangerment or neurotoxicity. (Reprinted with permission from: Wolkowitz et al. 2001)

Major depression may come about as an interplay of dysregulated (and inter-connected) neurotransmitter, hypothalamic peptide, adrenal steroid, neurosteroid and neurotrophic factor activities, some of which may culminate in CNS dysfunction or neurotoxicity (Figure 1). Also, it has become apparent (at least in pre-clinical models) that standard antidepressants share mechanisms beyond the monoamine synapse (Table 1); these alternate mechanisms may prove to be as important, if not more important, than the monoaminergic ones. An emerging model is that: (1) failure to adapt to stress, on a cellular if not a behavioural level, predisposes to or accompanies depression, and (2) medications that facilitate appropriate cellular adaptation or that attenuate the toxic sequellae of maladaptation are effective antidepressants. To the extent this model is true, multiple loci, not directly linked to increases in intra-synaptic monoamine concentrations, should prove useful in treating major depression (Figure 1) (Wolkowitz et al. 2001). Rather than supplanting the monoamine hypothesis, the newer models reviewed here complement it, and in many cases, interact with it. By broadening our mechanistic focus, we will hopefully also broaden our therapeutic power.

Owen M. Wolkowitz and Victor I. Reus

Correspondence:
Owen M. Wolkowitz, MD
UCSF Medical Center
401 Parnassus Ave., Box F-0984
San Francisco, CA 94143-0984, USA
Tel: +1 415 476 7433
Fax: +1 415 502 2661
E-mail: owenw@itsa.ucsf.edu

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