DEPRESSION GETS OLD FAST: DO STRESS AND DEPRESSION ACCELERATE CELL AGING?

Owen M. Wolkowitz, M.D.,1* Elissa S. Epel, Ph.D.,1 Victor I. Reus, M.D.,1 and Synthia H. Mellon, Ph.D.2

Depression has been likened to a state of “accelerated aging,” and depressed individuals have a higher incidence of various diseases of aging, such as cardiovascular and cerebrovascular diseases, metabolic syndrome, and dementia. Chronic exposure to certain interlinked biochemical pathways that mediate stress-related depression may contribute to “accelerated aging,” cell damage, and certain comorbid medical illnesses. Biochemical mediators explored in this theoretical review include the hypothalamic–pituitary–adrenal axis (e.g., hyper- or hypoactivation of glucocorticoid receptors), neurosteroids, such as dehydroepiandrosterone and allopregnanolone, brain-derived neurotrophic factor, excitotoxicity, oxidative and inflammatory stress, and disturbances of the telomere/telomerase maintenance system. A better appreciation of the role of these mediators in depressive illness could lead to refined models of depression, to a re-conceptualization of depression as a whole body disease rather than just a “mental illness,” and to the rational development of new classes of medications to treat depression and its related medical comorbidities.

Key words: depression; stress; aging; cortisol; BDNF; DHEA; telomeres; oxidation; inflammation; allopregnanolone

*Correspondence to: Owen M. Wolkowitz, 401 Parnassus Ave., Box F-0984, San Francisco, CA 94143-0984. E-mail: Owen.Wolkowitz@ucsf.edu

1Department of Psychiatry, University of California School of Medicine, San Francisco, California
2Department of OB-GYN and Reproductive Sciences, University of California School of Medicine, San Francisco, California

The authors disclose the following financial relationships within the past 3 years: Contract grant sponsors: O’Shaughnessy Foundation; University of California.

© 2010 Wiley-Liss, Inc.
cellular aging and damage and disease (Fig. 1). There is widespread recognition that certain physical stressors, such as oxidative and inflammatory stress, can accelerate aging in cells.\[17-21\] It has recently been appreciated that psychological stress can also prematurely age cells, possibly by invoking similar physical processes.\[15,20,22-32\] Major depression and its associated biological perturbations are the focus of this review. To the extent similar processes are seen in other conditions (e.g., chronic psychological stress, posttraumatic stress disorder, schizophrenia, certain neurodegenerative disorders, etc.), aspects of this model might also be applicable. Indeed, some of the data supporting this model were derived from chronically stressed, but not necessarily depressed, populations; such data will be identified in the text. In brief, stress-related dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, as moderated by genetic\[33-36\] and epigenetic\[37\] factors and by cognitive appraisal,\[38,39\] social support,\[40,41\] and coping styles,\[42,43\] leads to cortisol-induced changes in gene expression (including genes related to monoaminergic and peptidergic neurotransmission), neuroendangering or neurotoxic effects in certain brain areas (e.g., prefrontal cortex and hippocampus), excitotoxicity, oxidative stress, immune alterations leading to a proinflammatory milieu (or “neuroinflammation”), and accelerated cell aging (via effects on the telomere/telomerase maintenance system), as described below. In this context, normal compensatory or reparative processes are diminished, e.g., decreased counterregulatory neurosteroids (e.g., dehydroepiandrosterone [DHEA] and allopregnanolone), decreased antioxidant compounds (e.g., Vitamin C or E), diminished anti-inflammatory/immunomodulatory cytokines (e.g., IL-10), decreased activity of neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF]) and decreased activity or effectiveness of the telomere-lengthening enzyme, telomerase. The juxtaposition of enhanced toxic processes with diminished protective or restorative ones can culminate in cellular damage and physical disease\[44\] (Table 1). The presentation of this model here will be relatively concise, but related reviews of this and similar models are published elsewhere.\[20,22,23,36,45-53\] This review represents an update and refinement of models we have presented earlier.\[45-48\] This model is not meant to be complete or all-encompassing, nor is it meant to apply to all individuals with major depression, because different endophenotypes of depression could well have different underlying pathologic components.\[45,54,55\] Instead, this broadly sketched model is meant to highlight and connect certain interesting new findings in the study of stress and depression, and to provide testable hypotheses that could guide research and treatment in new directions.

GLUCOCORTICOID AND NEUROSTEROID

The physiological significance of increased circulating GC levels remains unknown, and it is even debatable whether “hypercortisolemia” results in net hypercortisol-ism at the cellular level, or rather in net
Inflammatory cytokines Anti-inflammatory/immunoregulatory cytokines
Free radicals (oxidative stress) Antioxidants
Intracytoplasmic calcium Intracellular glucose
Synaptic glutamate (excitotoxicity) Insulin sensitivity

GCs, can significantly affect individuals’ responses to
TNF-topically applied GCs) is inversely correlated with
peripheral GR sensitivity in depressed individuals
This possibility is supported by the finding that
hypo
c

= INCREASED

Hypercortisolemia (with hyper- or hypocortisolism)
Synaptic glutamate (excitotoxicity)
Intracytoplasmic calcium
Free radicals (oxidative stress)
Inflammatory cytokines

= DECREASED

Neurosteroids (allopregnanolone, DHEA)
Insulin sensitivity
Intracellular glucose
Antioxidants
Anti-inflammatory/immunoregulatory cytokines
Neurotrophic factors
Telomerase

\[a\]Evidence is mixed as to whether major depression is characterized by excessive or diminished levels of DHEA, but it is often low with psychological stress.
\[b\]Evidence is mixed as to whether the anti-inflammatory/immunoregulatory cytokine, IL-10, is elevated or diminished in major depression.
\[c\]Telomerase activity has been reported as low or high (albeit less effective in preserving telomere length) in chronic stress; there are as yet no published data on telomerase activity in major depression.

hypocortisolism, perhaps due to downregulation of the glucocorticoid receptor (GR) (referred to as “GC resistance”).\[45,56\] It is possible but not proven that hyper- and hypocortisolism identify different subtypes of depression or map onto different symptom clusters.\[45,54,57–59\] It should also be recognized that the effects of either state are likely to differ, depending on the target tissue involved and that “relative” conditions of either hyper- or hypocortisolism may exist at the same time within organisms, making any global statements a simplification of the underlying endocrine state.\[60–63\] For example, different GR polymorphisms can significantly affect individuals’ responses to GCs,\[35,64\] and alternative splicing of the GR mRNA can lead to different GR isoforms with different actions in different tissues.\[65,66\] Furthermore, early life events, such as childhood abuse, can epigenetically reprogram GR expression and splicing, leading to important inter-individual differences in GC responsivity.\[67\] The “hypocortisolism” hypothesis is supported by findings that proinflammatory cytokine levels (e.g., tumor necrosis factor [TNF]-\(\alpha\), IL-1\(\beta\), and IL-6) tend to be increased in the plasma of depressed patients, and that proinflammatory cytokines can contribute to depressive symptomatology. Because cortisol typically has anti-inflammatory actions and suppresses proinflammatory cytokines (although there are instances to the contrary),\[68–71\], the coexistence of elevated cortisol and proinflammatory cytokine levels suggests an insensitivity to cortisol at the level of the lymphocyte GR.\[72\] This possibility is supported by the finding that peripheral GR sensitivity in depressed individuals (assessed by cutaneous vasoconstrictive responses to topically applied GCs) is inversely correlated with TNF-\(\alpha\) concentrations.\[73\] The “hypocortisolism” hypothesis is also supported by recent genome-wide expression microarray analyses on monocytes from stressed (but not necessarily depressed) caregivers compared to controls.\[74\] Despite having similar cortisol secretory patterns, the caregivers in that study showed diminished expression of glucocorticoid response element transcripts and heightened expression of transcripts with response elements for NF-kappaB, a key proinflammatory transcription factor.

On the other hand, the “hypercortisolism” hypothesis is supported by phenotypic somatic features suggestive of cortisol excess and of increased end-organ cortisol signaling in depression, e.g., osteoporosis, insulin resistance, Type II diabetes, a relative hypokalemic alkalosis accompanied by neutrophilia and lymphocytosis, hypertension, metabolic syndrome and visceral/intra-abdominal adiposity (reviewed in Ref.\[45\]). Further support of net GC over-activation is provided by evidence of altered expression of target genes such as BDNF, which are believed to be under negative regulatory control by cortisol.\[75\] It remains debatable whether hypercortisolism is causally related to hippocampal atrophy often reported in depression.\[72,76–82\]

Pathologically elevated or diminished GC activity could, via genomic mechanisms, alter transcription of genes involved in synthesis and degradation of monoamine neurotransmitters and other substances,\[82–87\] and could have neurobehavioral sequelae.\[45\] Chronic hypercortisolemia, in particular, has been proposed by Sapolsky and others,\[14\] to result in a biochemical “cascade,” which can culminate in cell endangerment or cell death in certain hippocampal cells. In the simplest description of this model, GC excess engenders a state of intracellular glucoprivation (insufficient intracellular glucose energy stores) in certain cells, impairing the ability of glia and other cells to clear synaptic glutamate. The resulting excitotoxicity results in excessive release of calcium into the cytoplasm, which can contribute to oxidative damage, proteolysis, and cytoskeletal damage.\[88–90\] Unchecked, these processes can culminate in diminished cell viability or cell death. For example, GCs can, via non-genomic mechanisms, directly modulate mitochondrial calcium and oxidation in an inverted U-shaped manner, with chronically elevated levels leading to cellular damage.\[91\] In the present model, we expand upon these earlier GC models by integrating effects on neurotrophic factors, neurosteroids, inflammation, and

**TABLE 1. Possible detrimental changes seen in depression and/or chronic stress**

<table>
<thead>
<tr>
<th>(\uparrow) Potentially damaging mediators</th>
<th>(\downarrow) Potentially protective or restorative mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCREASED</strong></td>
<td><strong>DECREASED</strong></td>
</tr>
<tr>
<td>Hypercortisolemia (with hyper- or hypocortisolism)</td>
<td>Neurosteroids (allopregnanolone, DHEA)</td>
</tr>
<tr>
<td>Synaptic glutamate (excitotoxicity)</td>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td>Intracytoplasmic calcium</td>
<td>Intracellular glucose</td>
</tr>
<tr>
<td>Free radicals (oxidative stress)</td>
<td>Antioxidants</td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
<td>Anti-inflammatory/immunoregulatory cytokines(\text{b})</td>
</tr>
<tr>
<td></td>
<td>Neurotrophic factors</td>
</tr>
<tr>
<td></td>
<td>Telomerase(\text{c})</td>
</tr>
</tbody>
</table>

Review: Do Stress and Depression Accelerate Cell Aging?

Depression and Anxiety
the telomere/telomerase maintenance system, an important aspect of cell aging.

Although circulating cortisol concentrations are frequently elevated in depression, plasma and CSF concentrations of the GABA-A receptor agonist neurosteroid, allopregnanolone, are decreased in unmedicated depressives, plasma and CSF levels of allopregnanolone increase with selective serotonin reuptake inhibitor (SSRI) treatment in proportion to their antidepressant effect.\[92,93\] SSRI antidepressants rapidly increase allopregnanolone synthesis, and this may contribute to their anxiolytic effects.\[92,94,95\] Another neurosteroid, DHEA, which can have “anti-cortisol” effects (reviewed in\[96\]), and which promotes psychological resilience,\[51,97\] has been reported to be both high and low in depression,\[96\] but DHEA treatment is generally reported as having significant antidepressant effects.\[96\] Notably, both these neurosteroids modulate HPA,\[96\] BDNF\[96,98,99\] and immune\[3,100–102\] activity, antagonize oxidative stress\[103,104\] and have neuroprotective or neuroregenerative effects.\[96,98–101\] Allopregnanolone also inhibits stress-induced corticotropin-releasing hormone release.\[99\] Endogenous decreases in these neurosteroids or exogenously produced increases in their effects would be expected to have damaging or beneficial effects, respectively, in the context of depression or chronic stress.\[48,92,95,96,105,106\]

**IMMUNE FUNCTION**

Stress-related dysregulation of HPA axis and of GC activity also contributes to immune dysregulation in depression,\[107\] and proinflammatory cytokines further alter HPA axis activity.\[108,109\] Immune dysregulation may be an important pathway by which depression and chronic stress heighten the risk of serious medical comorbidity.\[20,30,124\] Several major proinflammatory cytokines, such as IL-1β, IL-2, IL-6, and TNF-α, are elevated in depression, either basally or in response to mitogen stimulation or acute stress.\[107,112,113\] Conversely, certain anti-inflammatory or immunomodulatory cytokines, such as IL-1 receptor antagonist and IL-10, may be increased or decreased or may be dysregulated relative to proinflammatory cytokines.\[112,114,115\] In particular, the ratio of proinflammatory to anti-inflammatory/immunomodulatory cytokines may be heightened in depression and could result in increased inflammation\[112\] and, subsequently, in increased free radical production and oxidative stress.\[116\] Converging findings suggest that high peripheral levels of inflammatory cytokines, such as IL-6, are associated with the activation of central inflammatory mechanisms that, under some circumstances, adversely affect the hippocampus, where IL-6 receptors are abundantly expressed.\[117\] Hippocampal neurogenesis is also suppressed by microglial activation, which leads to brain inflammation,\[118\] and high proinflammatory cytokine concentrations can contribute to hippocampal neurodegeneration.\[119\] In wild-type mice, stress increases hippocampal IL-6 concentrations, but IL-6 (−/−) knockout mice are resistant to stress-induced learned helplessness, an animal model of depression.\[120\] In healthy humans, plasma IL-6 concentrations are inversely correlated with hippocampal gray matter,\[121\] and elevated pre-treatment inflammatory cytokine levels predict poorer response to antidepressant medications in individuals with major depression.\[122\] High proinflammatory cytokine levels also directly contribute to monoamine dysregulation, HPA axis stimulation, depression, and cellular and organismic senescence.\[119,123\] It should be noted, however, that due to the complexity of cytokine actions in neurons and glia, the end effect of individual cytokines can be either detrimental or protective, depending on the circumstances.\[112\]

**OXIDATION**

Stress and altered HPA axis activity can also increase oxidative damage and decrease antioxidant defenses.\[20,29,46,124\] Oxidative stress, together with inflammatory cytokines, often increase with aging and in various disease states, whereas antioxidant and anti-inflammatory activities paradoxically decrease, resulting in a heightened likelihood of cellular damage and of a senescent phenotype.\[20,125\] Oxidative stress occurs when the production of oxygen-free radicals exceeds the capacity of the body's antioxidants to neutralize them. Oxidative stress damages DNA, protein, lipids, and other macromolecules in many tissues, with telomeres (discussed below)\[126\] and the brain\[90\] being particularly sensitive. Elevated plasma and/or urine oxidative stress markers (e.g., increased F2-isoprostanes and 8-hydroxydeoxyguanosine [8-OHdG] along with decreased antioxidant compounds, such as Vitamins C and E) have been reported in individuals with depression and in those with chronic psychological stress\[27,29,127,128\] and the concentration of peripheral oxidative stress markers is positively correlated with the severity and chronicity of depression,\[29,129,130\] as well as with evidence of accelerated apoptosis in polymorphonuclear blood cells.\[131\] Furthermore, the ratio of serum oxidized lipids (F2-isoprostanes) to antioxidants (Vitamin E) is directly related to psychological stress, and is inversely related to telomere length and telomerase activity (both discussed below) in chronically stressed caregivers.\[22\] Conversely, antidepressants decrease oxidative stress.\[132\] Because cellular oxidative damage is an important component of the aging process, prolonged or repeated exposure to oxidative stress could accelerate aspects of biological aging and promote aging-related comorbid diseases in depression.\[29\] For example, oxidative stress potentiates TNF-α-induced activation of the cell death cascade.\[133\] Stress- or depression-related increases in oxidative stress additionally blunt certain protective or reparative processes, because oxidative stress is inversely correlated with

*Depression and Anxiety*
telomerase activity as well as telomere length (discussed below), and because increased oxidative stress (and lower antioxidant protection) is associated with lower BDNF activity (discussed below).

**BRAIN-DERIVED NEUROTROPHIC FACTOR**

The “neurotrophic model” of depression posits that diminished hippocampal BDNF activity, caused by stress or excessive GCs, impairs the ability of stem cells in the subgranular zone of the dentate gyrus (as well as cells in the subventricular zone, projecting to the prefrontal cortex) to proliferate into mature cells that remain viable. It is not known whether such processes can cause depression and whether they are relevant to the mechanism of action of antidepressant drugs; evidence is somewhat stronger for BDNF involvement in antidepressant effects than in the etiology of depression. Furthermore, unmedicated patients with depression have decreased hippocampal (at autopsy) and serum concentrations of BDNF. A role of BDNF in antidepressant mechanisms of action is supported by findings that hippocampal neurogenesis (in animals) and serum BDNF concentrations (in depressed humans) increase with antidepressant treatment, and that hippocampal neurogenesis is required for behavioral effects of antidepressants in animals. Apart from its direct neurotrophic actions, BDNF also has anti-inflammatory and antioxidant effects and improves the efficiency of brain mitochondrial oxygen utilization, which may contribute to its neuroprotective efficacy. BDNF attenuates glucocorticoid-induced neuronal death, and BDNF activity synergizes with telomerase activity (discussed below) in promoting the growth of developing neurons.

**CELL AGING: TELOMERES AND TELOMERASE**

Telomeres are DNA-protein complexes that cap the ends of linear DNA strands, protecting DNA from damage. When telomeres reach a critically short length, as happens when cells undergo repeated mitotic divisions without adequate telomerase activity (e.g., immune cells and stem cells, including neurogenic stem cells in the hippocampus), cells become susceptible to apoptosis and death. Even in nondividing cells, such as mature neurons, telomeres can become shortened by oxidative stress, which preferentially damages telomeres to a greater extent than nontelomeric DNA. This non-mitotic type of telomere shortening also increases susceptibility to apoptosis and cell death. Telomere length is a indicator of “biological age” (as opposed to just chronological age) and represents a cumulative log of the number of cell divisions and a cumulative record of exposure to genotoxic and cytotoxic processes, such as oxidative stress, which preferentially damages telomeres in stressed caregivers (as well as cells in the subventricular zone, projecting to the prefrontal cortex) to proliferate into mature cells that remain viable. It is not known whether such processes can cause depression and whether they are relevant to the mechanism of action of antidepressant drugs; evidence is somewhat stronger for BDNF involvement in antidepressant effects than in the etiology of depression. Furthermore, unmedicated patients with depression have decreased hippocampal (at autopsy) and serum concentrations of BDNF. A role of BDNF in antidepressant mechanisms of action is supported by findings that hippocampal neurogenesis (in animals) and serum BDNF concentrations (in depressed humans) increase with antidepressant treatment, and that hippocampal neurogenesis is required for behavioral effects of antidepressants in animals. Apart from its direct neurotrophic actions, BDNF also has anti-inflammatory and antioxidant effects and improves the efficiency of brain mitochondrial oxygen utilization, which may contribute to its neuroprotective efficacy. BDNF attenuates glucocorticoid-induced neuronal death, and BDNF activity synergizes with telomerase activity (discussed below) in promoting the growth of developing neurons.

**DEPRESSION AND ANXIETY**

Telomerase is a reverse transcriptase enzyme that rebuilds telomere length, thereby delaying cell senescence, apoptosis, and cell death. Telomerase also has antiaging or cell survival-promoting effects independent of its effects on telomere length by regulating transcription of growth factors, synergizing with the neurotrophic effects of BDNF, having antioxidant effects and intrinsic antiapoptotic effects, protecting cells from necrosis, and stimulating cell growth in adverse conditions. Telomerase activity has not yet been characterized in individuals with major depression, but it has been reported to be diminished or increased in stressed caregivers compared to low stress controls. Several of the mediators discussed above can contribute to diminished telomere length and/or telomerase activity (e.g., cortisol, oxidative stress, and inflammatory cytokines), highlighting the interlinked nature of cell-damaging and cell-protective mediators.
DO STRESS AND DEPRESSION ACCELERATE CELL AGING?

We have briefly reviewed evidence of biochemical abnormalities in depression, some of which are consistent with an aged phenotype that could contribute to certain medical comorbidities seen with depression. They could also contribute to the depressive state itself, but that has not been adequately tested. In particular, depression (and perhaps chronic stress, as well) may be associated with increased cell damaging processes and decreased cell protective or restorative ones (Table 1). We propose a model in which these abnormalities are causally interlinked and may derive, directly or indirectly, from altered HPA axis and GC activity seen in depression (Fig. 1). It remains uncertain whether the brain in depressed individuals is subject to net hypo- or hypercortisolism, and even within the brain, individual component tissues, such as neurons and glia, may differ in their response to altered circulating GC levels as a result of differing receptor expression or metabolic enzymes.

We have couched this model in terms of "accelerated aging" at the cell level, although whether cell aging is actually accelerated in depression remains to be determined in prospective trials. It is important to recognize that this model is unlikely to apply to all individuals with depression (many of whom do not have discernible HPA axis dysregulation), and that many of these changes are not specific to major depression. Also, various genetic and epigenetic moderators, not discussed here, are undoubtedly important. The major importance of this hypothetical model is that it identifies certain nontraditional targets for pharmacological and nonpharmacological treatment, and thus could lead to new theory-driven therapies. In particular, treatments directed at the targets identified here have the potential not only to treat depression but also to treat certain medical comorbidities that occur alongside depression. Interestingly, even traditional antidepressant medications, which putatively work via monoaminergic actions, affect many of the novel targets described here (see Fig. 1), even though they were not developed with those purposes in mind. Last, the identification of novel biomarkers of depression may discriminate separate endophenotypes of depression that respond differently to different treatments, although some of the endocrinological and neurochemical differences reported may be dependent more on the target tissue examined than reflective of a global endophenotype. This will hopefully accelerate the era of personalized antidepressant treatment.

THEORETICAL MODEL AND NOVEL TREATMENT POSSIBILITIES

A schematic overview of our model is presented in Figure 1. The condensed and simplified nature of this schematic precludes depiction of numerous other mediators and moderators and interactions that are involved. Therefore, this depiction should be viewed as a "broad brush stroke" theoretical model. The bracketed numbers in Figure 1 are keyed to potential sites of therapeutic intervention described below. In this model, elevated cortisol levels are associated with downregulation of GRs ("GC resistance"); the "net" GC activity remains uncertain and could even differ in different tissues. A deficit in GR function can precede or result from the hypercortisolism. To the extent that lymphocyte GRs become GC resistant, immune function is altered and excessive proinflammatory cytokine effects can occur. Changes in cortisol activity also result in multiple genomic changes, e.g., altered levels of certain neurotransmitters (e.g., decreased serotonin and increased dopamine activity in certain brain regions, which could contribute to depressive or psychotic symptoms). To the extent GC activity is "excessive" in certain brain regions, a cascade of events can follow, characterized by diminished insulin signaling, intraneuronal glucoprivation and diminished energy availability, defective clearance of intrasynaptic glutamate, excitotoxicity, intracellular buildup of calcium, generation of oxygen-free radicals (oxidative stress), diminution of telomerase activity and cellular damage or cell death. Increased oxidative stress can damage the enzyme telomerase and shorten telomeres, at least in certain cells in the body. In nondepressed individuals, leukocyte telomere shortening is associated with a host of physical illnesses and premature mortality. If this occurs in depressed individuals as well, it could help explain the surfeit of medical illness and the shortened life expectancy seen with chronic depression. Chronic stress and depression and/or excessive cortisol exposure can also be associated with underproduction of certain counterregulatory neurosteroid hormones, e.g., DHEA and allopregnanolone, which could further dysregulate HPA axis activity, hamper antioxidative function, and reduce neuroprotective capacity. Additionally, prolonged stress and/or increased cortisol activity can downregulate BDNF activity, which further diminishes neuroreparative capacity and attenuates neurogenesis.

To the extent this theoretical model is accurate, several potential treatment loci emerge, as indicated numerically in Figure 1: (1) traditional antidepressants have several novel functions apart from increasing intrasynaptic monoamine concentrations: they up-regulate...
GR function, increase allopregnanolone synthesis (certain SSRIs), and have anti-inflammatory and antioxidant effects; (2) CRH antagonists, (3) stress reduction, meditation, and other behavioral and lifestyle interventions; (4) antiglucocorticoids; (5) energy supplementation or insulin receptor sensitizers; (6) glutamate antagonists; (7) calcium blockers and antioxidants; (8) DHEA; (9) 3-α-hydroxy–steroid dehydrogenase (3-α-HSD) stimulators (including SSRIs), which increase allopregnanolone synthesis; (10) environmental enrichment, exercise; (11) BDNF administration via novel routes of administration; (12) telomerase activation and (13) anti-inflammatory drugs, TNF-α antagonists, etc. It is possible that, by targeting such “upstream” mediators of the biochemical milieu, additional therapeutic leverage might be gained. Already, preliminary studies are testing many of these strategies, with preliminary signs of success.

Acknowledgments. The authors acknowledge the generosity of the O’Shaughnessy Foundation, which supplied major funding. Additional funding was supplied by the University of California, San Francisco, Academic Senate. The authors are also grateful to Dr. Wolkowitz, a pioneer in the field of cell aging, whose generosity has been indispensable.

Financial disclosures: Dr. Wolkowitz has received lecture honoraria from Jazz Pharmaceuticals and Merck Pharmaceuticals, and has served on an Advisory Board for Pfizer Pharmaceuticals. No other authors have financial ties to these or any other pharmaceutical companies.

REFERENCES


77. Lucassen PJ, Heine VM, Müller MB et al. Stress, depression and hippocampal apoptosis. CNS Neurol Disord Drug Targets 2006;5:531–546.


82. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–935.


95. Guidotti A, Costa E. Can the antidepressive and anxiolytic profiles of selective serotonin reuptake inhibitors be related to their ability to increase brain allopregnanolone availability? Biol Psychiatry 1998;44:865–873.


127. Grant MM, Barber VS, Griffiths HR. The presence of ascorbate induces expression of brain derived neurotrophic factor in SH-SY5Y neuroblastoma cells after peroxide insult, which is associated with increased survival. Proteomics 2005;5:534–540.


203. Zhang Y, Partridge WM. Conjugation of brain-derived neurotrophic factor to a blood-brain barrier drug targeting system enables neuroprotection in regional brain ischemia following intravenous injection of the neurotrophin. Brain Res 2001;889:49–56.
204. Egleton RD, Davis TP. Development of neuropeptide drugs that cross the blood-brain barrier. NeuroRx 2005;2:44–53.