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Of sound mind and body: depression, disease, and accelerated aging

Owen M. Wolkowitz, MD; Victor I. Reus, MD; Synthia H. Mellon, PhD

Major Depressive Disorder (MDD) is typically considered a mental illness, yet pathology associated with MDD is evident in cells and organs throughout the body. For example, MDD is associated with an increased risk of developing atherosclerosis, heart disease, hypertension, stroke, cognitive decline, and dementia (including Alzheimer's disease), osteoporosis, immune impairments (eg, "immunosenescence"), obesity, metabolic syndrome, insulin resistance, and type 2 diabetes,¹⁻⁴ and individuals who are afflicted both by MDD and one of these diseases have a poorer prognosis than individuals afflicted by either alone.³ This increased risk of serious

Major depressive disorder (MDD) is associated with a high rate of developing serious medical comorbidities such as cardiovascular disease, stroke, dementia, osteoporosis, diabetes, and the metabolic syndrome. These are conditions that typically occur late in life, and it has been suggested that MDD may be associated with "accelerated aging." We review several moderators and mediators that may accompany MDD and that may give rise to these comorbid medical conditions. We first review the moderating effects of psychological styles of coping, genetic predisposition, and epigenetic modifications (eg, secondary to childhood adversity). We then focus on several interlinked mediators occurring in MDD (or at least in subtypes of MDD) that may contribute to the medical comorbidity burden and to accelerated aging: limbic-hypothalamic-pituitary-adrenal axis alterations, diminution in glucocorticoid receptor function, altered glucose tolerance and insulin sensitivity, excitotoxicity, increases in intracellular calcium, oxidative stress, a proinflammatory milieu, lowered levels of "counter-regulatory" neurosteroids (such as allopregnanolone and dehydroepiandrosterone), diminished neurotrophic activity, and accelerated cell aging, manifest as alterations in telomerase activity and as shortening of telomeres, which can lead to apoptosis and cell death. In this model, MDD is characterized by a surfeit of potentially destructive mediators and an insufficiency of protective or restorative ones. These factors interact in increasing the likelihood of physical disease and of accelerated aging at the cellular level. We conclude with suggestions for novel mechanism-based therapeutics based on these mediators.

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Selected abbreviations and acronyms

5-HT	<i>serotonin</i>
BDNF	<i>brain-derived neurotrophic factor</i>
CRH	<i>corticotrophin-releasing hormone</i>
DHEA	<i>dehydroepiandrosterone</i>
GC	<i>glucocorticoid</i>
GR	<i>glucocorticoid receptor</i>
IL	<i>interleukin</i>
LHPA	<i>limbic-hypothalamic-pituitary-adrenal axis</i>
MDD	<i>major depressive disorder</i>
PMDD	<i>premenstrual dysphoric disorder</i>

medical diseases is not fully explained by lifestyle choices such as diet, exercise, and smoking, and the reasons for the heightened risk remain unknown.⁴ Moreover, many of the medical comorbidities seen in MDD are diseases more commonly seen with advanced age, and MDD has even been characterized as a disease of “accelerated aging.”^{1,5,6} In this review article, we explore certain biological mediators that are dysregulated in MDD and that may contribute to the depressed state itself, to the comorbid medical conditions, and to “accelerated aging.” Discovering novel pathological mediators in MDD could help identify new targets for treating depression and its comorbid medical conditions and could help reclassify MDD as a multisystem disorder rather than one confined to the brain.

Theoretical model

We propose a model of MDD comprised of certain pathogenic processes that are interlinked and often recursive, that occur in the brain and in the periphery, and that can culminate in cellular damage, cellular aging, and disease.⁶⁻¹⁰ This model is presented schematically in *Figure 1* and is briefly described in this introduction; the individual moderators and mediators are described in greater detail in the remainder of this article. This model is not intended to be complete or all-encompassing but is meant to highlight and connect certain interesting findings in the study of depression. It does not propose that each component is necessary or sufficient, or that the specified mediators are the sole routes to MDD. It also does not speak to the directions of causality between depression and physical pathology. Further, many of the specified mediators may serve either protective or destructive functions depending on their context and chronicity.¹¹⁻¹³ Nonetheless, the model presented

Figure 1. Model of multiple pathways leading to psychiatric and physical illness and cell aging. In conjunction with genetic and epigenetic moderators, elevated cortisol levels, associated with downregulation of glucocorticoid receptor (GC) function (GC resistance) may result in altered immune function, leading to excessive synthesis of proinflammatory cytokines. Changes in glucocorticoid-mediated activities also result in genomic changes (altered levels of certain neurotransmitters, neurotrophins, and other mediators), as well as dysregulation of the limbic-hypothalamic-pituitary adrenal (LHPA) axis that might contribute to neuroendangerment or neurotoxicity, perhaps leading to depressive or cognitive symptoms. Dysregulation of the LHPA axis can also lead to intracellular glucose deficiency, glutamatergic hyperactivity, increased cellular calcium concentrations, mitochondrial damage, free radical generation, and increased oxidative stress. This cascade of events, coupled with a milieu of increased inflammatory cytokines, may lead to accelerated cellular aging via effects on the telomere/telomerase maintenance system. Dysregulation of normal compensatory mechanisms, such as increased neurosteroid or neurotrophin production, may further result in inability to reduce cellular damage, and thereby exacerbate destructive processes. This juxtaposition of enhanced destructive processes with diminished protective/restorative processes may culminate in cellular damage, apoptosis, and physical disease. Allopreg, allopregnanolone; BDNF, brain-derived neurotrophic factor; CRH, corticotrophin releasing hormone; DHEA, dehydroepiandrosterone; GR, glucocorticoid receptor

here provides testable hypotheses for further investigation and provides rationales for considering novel treatment approaches. Earlier reviews of this model have been published elsewhere.^{5,6,10}

In brief, psychological and physical stressors trigger physiological responses that are acutely important for successful adaptation to the stress ("stress arousal"). However, when stress responses are disrupted or inappropriately prolonged, endangering effects may supersede the protective ones. The "cost" to the organism of maintaining these physiological responses over prolonged periods has been termed "allostatic load"¹³ or "arousal pathology,"¹⁴ and it has repeatedly been associated with poor medical outcomes.¹² In addition to chronicity of the stress response, certain psychological, environmental, genetic, and epigenetic circumstances (discussed below) favor dysregulation of two main stress response effectors, the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and the locus coeruleus noradrenergic (NE) system.¹⁵ A particular problem may arise when these two systems, which are generally counter-regulatory, activate one another for prolonged periods of time (as may be seen in melancholic depression).¹⁵ The failure of glucocorticoids (GCs) to effectively counter-regulate stress-induced NE and LHPA activity may underlie critical aspects of MDD.¹⁵ Prolonged LHPA axis dysregulation can lead to neuroendangering or neurotoxic effects in vulnerable brain regions (eg, prefrontal cortex and hippocampus).¹⁶ It can also lead to energetic disturbances (decreased intracellular glucose availability and insulin resistance), glutamatergic hyperactivity/excitotoxicity, increased intracellular calcium concentrations, mitochondrial damage, free radical generation and oxidative stress, immune alterations (leading to a proinflammatory milieu), and accelerated cell aging (via effects on the telomere/telomerase maintenance system). The nature of cortisol abnormalities in MDD is complex, however, and will be discussed below. Prolonged activation of central NE systems, as often seen in melancholic depression, may be associated with worsened outcome in cardiovascular diseases and with accelerated cell aging at the level of the telomere.^{9,15}

In addition to increases in these destructive processes, normal compensatory or reparative processes may be diminished, eg, diminution of counter-regulatory neurosteroids, eg, dehydroepiandrosterone (DHEA),¹⁷ and allopregnanolone,¹⁸ decreased antioxidant compounds, diminished anti-inflammatory/immunomodulatory cytokines,

decreased neurotrophic factor concentrations, eg, brain-derived neurotrophic factor (BDNF), and altered telomerase activity. This juxtaposition of enhanced destructive processes with diminished (or inadequate) protective or restorative ones can culminate in cellular damage and physical disease (*Table I*). This model will be explored in greater depth in the following sections.

Moderators

Psychological stress and individual differences

Psychological stress is frequently a precipitant of depressive episodes,¹⁹ and under certain circumstances it can initiate the biochemical cascade described here.^{7,8,10,13,16,20} It is apparent, though, that individuals respond very differently to stress, due, in part, to differences in coping strategies, disposition, temperament, and cognitive attributional styles.²¹⁻²³ These can moderate stress-associated biological changes such as LHPA axis arousal,²³ inflammation,^{22,24} neurogenesis,²⁵ amygdala arousal,²⁶ and cell aging. In the first study examining a personality trait and telomere length, O'Donovan et al found that pessimism was related to shorter telomere length, as well as higher IL-6 concentrations.²² In a study of the effects of early-life parental loss on later-life depression, the quality of the family and home's adaptation to the loss was the single most power-

Potentially damaging mediators Increased	Potentially protective mediators Decreased
<ul style="list-style-type: none"> • Hyperactive LHPA axis and hypercortisolemia (with net hypercortisolism or hypocortisolism) • Synaptic glutamate and excitotoxicity • Intracytoplasmic calcium • Free radicals with oxidative stress • Inflammatory cytokines 	<ul style="list-style-type: none"> • Neurosteroids (eg, DHEA* and allopregnanolone) • Insulin sensitivity • Intracellular glucose • Antioxidants • Anti-inflammatory/immunomodulatory cytokines** • Neurotrophic factors (eg, BDNF) • Telomerase***

Table I. Possibly damaging and protective mediators in major depression. LHPA, limbic-hypothalamic-pituitary-adrenal; DHEA, dehydroepiandrosterone; BDNF, brain-derived neurotrophic factor. * Evidence is mixed as to whether DHEA concentrations are elevated or lowered in depression. ** Evidence is mixed as to whether the anti-inflammatory/immunomodulatory cytokine, IL-10, is elevated or lowered in depression. *** Evidence is mixed as to whether telomerase activity is elevated or lowered in states of chronic stress and depression.

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ful predictor of adult psychopathology, and was more important than the loss itself.²⁷ Biochemical aspects of resilience vs stress vulnerability will not be covered here but have recently been reviewed.²⁸

Adverse childhood events

Alexander Pope noted in 1734, that “as the twig is bent, the tree is inclined.” A rapidly expanding body of evidence suggests that early-life adversity (such as parental loss, neglect, and abuse) predisposes to adult depression^{27,29} as well as to LHPA axis hyper-reactivity to stress,^{27,30} increased allostatic load,^{13,31} diminished hippocampal volume (although this is controversial),³² lower brain serotonin transporter binding potential,³³ and a myriad of adult physical diseases.³⁴ Childhood adversity also predisposes to alterations in many of the mediators presented in our model of stress/depression/illness/cell aging, such as: inflammation,^{35,36} oxidative stress,³⁷ neurotrophic factors,³⁸ neurosteroids,³⁹ glucose/insulin/insulin-like growth factor (IGF-1) regulation,⁴⁰ telomerase activity,⁴¹ and telomere length.^{36,42-44} Alterations in LHPA axis activity (increased or decreased) have been well described in victims of childhood adversity, even when the individuals are not currently depressed.^{27,30} In fact, several instances of neurobiological changes reported in MDD may be more attributable to histories of early-life adversity,^{30,32} which are over-represented among individuals with MDD, than to the MDD itself. Thus, early-life adversity seems capable of “reprogramming” the individual to a certain lifetime repertoire of altered physiological responses to stress and to vulnerability to psychiatric and physical illness. This reprogramming toward stress arousal and preparedness may be adaptive when the individual is likely to be confronted with a lifetime of continuous adversity, but is clearly disadvantageous otherwise. The causes of early adversity-induced behavioral and biochemical changes, and the explanation for the very long-lasting effects of such adversity, are the subject of intense investigation. One explanation that has attracted much attention is epigenetic changes,^{45,46} discussed in the next section.

Genetic and epigenetic moderators

A number of variants in candidate genes have been implicated in contributing to maladaptive and resilient responses that underlie alterations in neuronal plastic-

ity and subsequent behavioral depression.⁴⁷ Evidence is strongest for genes involved in HPA regulation and stress (corticotrophin-releasing hormone [CRH]1; glucocorticoid receptor [GR]), regulatory neurotransmitters, transporters, and receptors (serotonin (5-HT)1A, 5-HT2, 5-HTTLPR, NET), neurotrophic factors, (brain-derived neurotrophic factor [BDNF], nuclear factor-kappaB, mitogen-activated protein kinase-1) and transcription factors (cAMP response element binding, Re-1 silencing transcription factor, delta FosB), but variations in other secondary modulatory factors (γ -aminobutyric acid [GABA], catechol-O-methyl transferase, monoamine oxidase, dynorphin, neuropeptide-Y) have also been hypothesized to be important in determining individual differences in stress response.⁴⁸ Studies of the CRH-1 gene in humans, for example, have shown that specific variants are associated with differential hormonal responses to stress, and with differing rates of depression and suicidal behavior.⁴⁹ Increasingly, such genetic effects have themselves been found to be modulated by individual variation in environmental context and history (gene x environment, GxE).⁴⁵ Epigenetics, which focuses on nongenomic alterations of gene expression, provides a mechanism for understanding such findings, through alteration of DNA methylation and subsequent silencing of gene expression or through physical changes in DNA packaging into histones.⁵⁰ A comprehensive review of this literature is beyond the scope of this article, but the findings of selective recent studies in these areas are illustrative of the regulatory complexity that influences the possible translation of stressful experiences into depression. Long-lasting epigenetic effects of early life experience on hypothalamic-pituitary-adrenal (HPA) responses have been demonstrated most clearly in animal models of differential maternal behavior and social isolation.^{45,46} Augmented maternal care was associated with reduced hypothalamic response to stress in rat pups and altered expression of CRH into adulthood.⁵¹ Suggestive human data compatible with these mechanisms have been reported.^{28,52} Oberlander et al,⁵³ for example, found that prenatal exposure to third trimester maternal depression was associated with increased methylation of the glucocorticoid receptor gene at 3 months of age in the newborn child, while McGowan⁴⁵ reported decreased levels of GR expression in the hippocampus of suicide victims with a history of childhood abuse, in comparison with those without such history and to controls. Tyrka and col-

leagues⁵⁴ have also shown that variants in the CRH1 receptor gene appear to interact with a history of childhood abuse in determining cortisol response to CRH. A separate body of research has focused on genetic investigations in components of serotonergic function, most commonly on a variant in the serotonin promoter (5-HTTLPR), and, to a lesser extent, on serotonin receptor genes.⁵⁵ In a small-scale study that remains controversial, Caspi et al⁵⁶ reported that the effect of a variant in 5-HTTLPR on increasing risk of depression was dependent upon a history of previous life stresses; several large-scale attempts at replication failed to support these conclusions and subsequent meta-analyses have been both positive and negative.^{57,58} Ressler et al⁵⁹ have suggested that gene x gene x environment interactions may be involved, and reported that 5-HTTLPR alleles interacted with CRH1 haplotypes and child abuse history in predicting depressive symptoms. Others, however, have found it hard to demonstrate such effects.⁵⁵ Yet another example of a potential GxGxE interaction was found in a study by Kauffman et al⁶⁰ of child abuse victims, in whom BDNF and 5-HTTLPR genotypes interacted with maltreatment history in predicting depression, with social support showing some moderating influence. Despite the persuasive empirical animal data, the clinical relevance of epigenetic effects of stress on human emotional behavior is yet to be convincingly established.

Biochemical mediators

Glucocorticoids

Elevated circulating GC levels are often observed in depressed individuals (especially in those with severe, melancholic, psychotic, or inpatient depressions), although considerable variability exists between studies, between individuals, and even within individuals over time, and some individuals are even hypocortisolemic.^{61,62} The physiological significance of increased circulating GC levels remains unknown, and it is debatable whether hypercortisolemia results in *hypercortisolism* at the cellular level, or, rather, in *hypocortisolism*, perhaps due to downregulation of the GR (often referred to as “GC resistance”).²⁰ Thus, determination of “net” GC activity in depressed individuals at the intracellular level has remained elusive.^{63,64} In fact, different subclasses of depressed individuals may show opposite patterns of limbic-hypothalamic-pituitary-adrenal (LHPA) axis

activity,¹⁵ and levels of LHPA activation may be more related to individual depressive symptoms than to the depressive syndrome per se.⁶⁵ Further, it is possible that both hypo- and hypercortisolism are related to depression, in an inverted-U shaped manner.⁶² Complicating our understanding of this issue, novel treatment strategies that decrease *or* increase GC activity may show antidepressant effects in certain patients.⁶⁶⁻⁶⁹ The “hypocortisolism” hypothesis is supported by findings that proinflammatory cytokine levels (eg, tumor necrosis factor [TNF]- α , interleukin [IL]-1 β and IL-6) tend to be increased in the serum of depressed patients, and that proinflammatory cytokines may contribute to depressive symptomatology. Since cortisol typically has anti-inflammatory actions and suppresses proinflammatory cytokines (although there are instances to the contrary [eg, ref 70]), the coexistence of elevated cortisol and elevated proinflammatory cytokine levels suggests an insensitivity to cortisol at the level of the lymphocyte GR.²⁰ Further supporting this notion, inflammatory cytokines downregulate GRs.²⁰ Also, antidepressants typically increase GR binding activity,²⁰ although in so doing, negative feedback onto the HPA axis is increased.⁷¹ On the other hand, the “hypercortisolism” hypothesis is supported by certain phenotypic somatic features suggestive of cortisol excess and end-organ cortisol receptor overactivation in some individuals with depression, eg, osteoporosis, insulin resistance, type 2 diabetes, a relative hypokalemic alkalosis accompanied by neutrophilia and lymphocytosis, hypertension, metabolic syndrome, and visceral/intra-abdominal adiposity.^{72,73} Further support of net GC overactivation is provided by evidence of altered expression of target genes such as BDNF, which are believed to be under negative regulatory control by cortisol.⁷⁴ Pathologically elevated *or* diminished GC activity might have adverse neurobehavioral and physical health sequelae.^{72,75} Chronic hypercortisolemia, in particular, has been proposed by Sapolsky and others¹⁶ to result in a biochemical “cascade,” which can culminate in cell endangerment or cell death in certain cells, including cells in the hippocampus. 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 influx and release of calcium into the cytoplasm, which contributes to oxida-

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tive damage, proteolysis, and cytoskeletal damage. Unchecked, these processes can culminate in diminished cell viability or cell death.

Neurosteroids

Although cortisol concentrations are often reported as elevated in depression, CSF concentrations of the potent GABA-A receptor agonist neurosteroid, allopregnanolone, are decreased in unmedicated depressives, and CSF levels of allopregnanolone increase with treatment in direct proportion to the antidepressant effect.⁷⁶ Selective serotonin reuptake inhibitor (SSRI) antidepressants rapidly increase allopregnanolone synthesis, and this may contribute to their anxiolytic effects.^{77,78} Another neurosteroid, DHEA, which may have “anti-cortisol” effects, has been reported to be both high and low in depression.¹⁷ Notably, both of these neurosteroids modulate HPA axis activity^{17,18} and immune system activity,^{17,79} antagonize oxidative stress^{17,80} and have certain neuroprotective effects.^{17,81} Depressed patients entering remission show decreases in plasma cortisol concentrations along with increases in plasma allopregnanolone concentrations.⁸² Endogenous decreases in this neurosteroid concentrations or exogenously produced increases in their concentrations might be expected to have damaging or beneficial effects, respectively, in the context of depression,^{17,78,83,84} and treatment trials have demonstrated significant antidepressant effects of exogenously administered DHEA.¹⁷ Animal models suggest that 3 α hydroxy-5 α reduced steroids (allopregnanolone and allotetrahydrodeoxycorticosterone) are responsive to stress⁸⁵ and may function to restore normal γ -aminobutyric acid (GABA)-ergic and hypothalamic-pituitary-adrenal function following stress.^{18,85} In vitro, allopregnanolone suppresses release of gonadotropin-releasing hormone⁸⁶ or CRH⁸⁷ via a GABA-A mediated mechanism. Allopregnanolone or allotetrahydrodeoxycorticosterone can also attenuate stress-induced increases in plasma ACTH and corticosterone and can affect arginine vasopressin transcription in the hypothalamus (paraventricular nucleus).¹⁸ Under chronic stress or in psychiatric disorders, dysregulation of the HPA axis could be exacerbated if there is insufficient activity of these “counter-regulatory” neurosteroids. In addition to protection against acute or chronic stress, neurosteroids such as allopregnanolone and allotetrahydrodeoxycorticosterone may be neuroprotective

against early life stressors⁸⁸ or against deleterious effects of social isolation.⁸⁹ In this way, these neurosteroids may be neuroprotective during development and may affect future responsiveness to stress.

The detrimental effects of neurosteroid dysregulation on stress responses has been particularly documented in women with premenstrual dysphoric disorder (PMDD).^{90,91} PMDD is a depressive disorder that is characterized by cyclic recurrence, during the luteal phase of the menstrual cycle, of a variety of physical and emotional symptoms that are so severe as to interfere with daily activities. In these studies in women with PMDD, both high and low concentrations of allopregnanolone during the luteal phase of the menstrual have been reported. However, women with PMDD have reduced responsiveness to neurosteroids (on GABA-A receptors)⁹² as well as a blunted stress response (failing to demonstrate an increase in allopregnanolone concentrations after acute stress) in women with PMDD and a prior history of depression.⁹⁰ Furthermore, women with PMDD who also had prior histories of depression showed significant decreases in allopregnanolone after acute stress.⁹⁰ These data highlight that long-term histories of depression may be associated with persistent, long-term effects on the responsivity of the neurosteroid system, as well as long-term effects on modulation of the HPA axis following stress.

Glucose and insulin regulation

Abnormalities of glucose homeostasis (eg, insulin resistance and impaired glucose tolerance) are seen in MDD, even in individuals who are nonobese and not diabetic.⁹³ These glucose and insulin abnormalities are most pronounced in hypercortisolemic depressed individuals,⁹⁴ as would be predicted based on cortisol's well-known anti-insulin effects. Hypercortisolemic depressives, compared with normocortisolemic ones, are also at increased risk of having increased abdominal (visceral) fat deposition⁹⁵ and the metabolic syndrome,⁹⁶ which are also risk factors for cardiovascular disease. Insulin resistance and diminished cellular glucose uptake can also lead to a dangerous “energetic crisis.”^{77,16} When this occurs in the hippocampus,¹⁶ for example, hippocampal excitotoxicity may develop, since there is insufficient energy available to clear glutamate from the synapse. Thereafter, cytosolic calcium is mobilized, triggering oxygen free radical formation and cytoskeletal proteolysis. The relevance of this in humans

was demonstrated in a PET scan study, in which cortisol administration to normal individuals resulted in significant reductions in hippocampal glucose utilization.⁹⁷ The importance of hippocampal insulin resistance for depression and cognitive disorders (eg, Alzheimer's disease) is the subject of active investigation.^{98,99}

Over and above these direct effects on energy balance, prolonged exposure to glucose intolerance and insulin resistance is associated with accelerated biological aging^{7,100} including shortened telomere length,¹⁰¹ and visceral adiposity is associated with increased inflammation and oxidation,^{102,103} both of which, themselves, promote accelerated biological aging.⁷ These will be further discussed below in the sections on inflammation, oxidation, and cell aging.

Immune function

Dysregulation of the LHPA axis contributes to immune dysregulation in depression, and immune dysregulation, in turn, can activate the HPA axis and precipitate depressive symptoms.²⁰ Immune dysregulation may be an important pathway by which depression heightens the risk of serious medical comorbidity.^{7,104,105} Several major proinflammatory cytokines, such as IL-1 β , IL-2, IL-6 and TNF- α , are elevated in depression, either basally or in response to mitogen stimulation or acute stress.^{20,106,107} Conversely, certain anti-inflammatory or immunomodulatory cytokines, such as IL-1 receptor antagonist and IL-10 may be decreased or dysregulated.¹⁰⁶ Indeed, the ratio of proinflammatory to anti-inflammatory/immunomodulatory cytokines may be disturbed in depression and could result in net increased inflammatory activity¹⁰⁶ as well as in oxidative stress.¹⁰⁸ Converging findings suggest that high peripheral levels of inflammatory cytokines, such as IL-6, are associated with the activation of central inflammatory mechanisms that can adversely affect the hippocampus, where IL-6 receptors are abundantly expressed.¹⁰⁹ High proinflammatory cytokine levels, for example, may directly contribute to depression, decreased neurotrophic support, and altered glutamate release/reuptake and hippocampal neurodegeneration,¹¹⁰ and, plasma IL-6 levels are inversely correlated with hippocampal gray matter in healthy humans.¹¹¹ Further, inappropriately and chronically elevated proinflammatory cytokines can contribute to accelerated biological aging (eg, premature shortening of immune cell telomeres¹¹²). Interestingly, the development of immunosenescence (eg,

the loss of the CD28 marker from CD8⁺ T cells), can further aggravate the proinflammatory milieu, since CD8⁺CD28⁺ cells hypersecrete IL-6.¹¹³ It should be noted, however, that due to the complexity of cytokine actions in neurons and glia, the end effect of individual cytokines may be either detrimental or protective, depending on the circumstances.¹⁰⁶

Oxidation

Stress and increased LHPA axis activity can also increase oxidative stress and decrease antioxidant defenses.^{5,7,114} Oxidative stress often increases with aging and various disease states, while antioxidant and anti-inflammatory activities decrease, resulting in a heightened likelihood of cellular damage and of a senescent phenotype.^{7,115} The co-occurrence of oxidative stress and inflammation (the so-called "evil twins" of brain aging¹¹⁵), as may be seen in depression, post-traumatic stress disorder (PTSD), stroke, Alzheimer's disease, and others, can be especially detrimental. Oxidative stress occurs when the production of oxygen free radicals (and other oxidized molecules) 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) and the brain being particularly sensitive. Elevated plasma and/or urine oxidative stress markers (eg, increased F2-isoprostanes and 8-hydroxydeoxyguanosine [8-OHdG], along with decreased antioxidant compounds, such as Vitamin C, Vitamin E, and Coenzyme Q) have been reported in individuals with depression and in those with chronic psychological stress, and the concentration of peripheral oxidative stress markers is positively correlated with the severity and chronicity of depression.^{114,116} Further, the ratio of serum oxidized lipids (F2-isoprostanes) to antioxidants (Vitamin E) is directly related to psychological stress.⁸ Importantly, this ratio (and the ratio of F2-isoprostanes to another antioxidant, Vitamin C) is inversely related to telomere length in chronically stressed caregivers⁸ and in individuals with major depression.¹¹⁷ Oxidative stress markers are also correlated with decreased telomerase activity.¹¹⁸ Further, diminished levels of antioxidants reportedly lower BDNF activity.¹¹⁹ Interestingly, antidepressants decrease oxidative stress.¹²⁰ Since cellular oxidative damage may be an important component of the aging process, prolonged or repeated exposure to oxidative

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stress might accelerate aspects of biological aging and promote the development of aging-related diseases in depressed individuals.¹¹⁴ It is unknown whether antioxidant treatment would retard stress- or depression-related aging; this is discussed below under “novel treatment implications.”

Brain-derived neurotrophic factor

The “neurotrophic model” of depression⁷⁴ emphasizes the centrality of neurogenesis and neuronal plasticity in the pathophysiology of depression. It 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 remain viable and to proliferate into mature cells. It is not known whether such effects can cause depression, but they may be relevant to the mechanism of action of antidepressant treatments.¹²¹ Unmedicated patients with depression have decreased hippocampal (at autopsy) and serum concentrations of BDNF.^{121,122} Over 20 studies have documented decreased serum concentrations of BDNF in unmedicated depressed individuals; this is now one of the most consistently replicated biochemical findings in major depression.^{121,123} Further, serum BDNF concentrations increase with antidepressant treatment.^{121,123} The relationship of peripheral BDNF concentrations to central ones is not known, but even peripherally administered BDNF abrogates depressive and anxiety-like behaviors and increases hippocampal neurogenesis in mice, suggesting that serum BDNF concentrations are functionally significant for brain function and are more than merely a biomarker.¹²⁴ 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,^{121,123} and that hippocampal neurogenesis and intact BDNF expression are required for behavioral effects of antidepressants in animals.^{125,126} Apart from its direct neurotrophic actions, BDNF also has anti-inflammatory and antioxidant effects that may contribute to its neuroprotective efficacy,¹²⁷ and BDNF, in concert with telomerase (discussed below) promotes the growth of developing neurons.¹²⁸ In addition, BDNF (despite its name) has significant peripheral actions that are important for physical health, and the low levels of

BDNF seen in MDD may be involved in certain comorbid illnesses such as cardiovascular disease, diabetes, obesity, and metabolic syndrome.¹²⁹ For example, BDNF improves glucose and lipid profiles, enhances glucose utilization, suppresses food intake, has an insulinotropic effect and protects cells in the islets of Langerhans (reviewed in ref 129). Plasma levels of BDNF are low in type 2 diabetes and are inversely correlated with fasting glucose levels.¹²⁹ Indeed, BDNF is increasingly considered not only a neurotrophin but a metabotrophin,¹²⁹ and its dysregulation has been proposed as a unifying feature of several clustered conditions, such as MDD, Alzheimer’s disease, and diabetes.¹³⁰

Cell aging: telomeres and telomerase

Telomeres are DNA-protein complexes that cap the ends of linear DNA strands, protecting DNA from damage.¹³¹ When telomeres reach a critically short length, as may happen when cells undergo repeated mitotic divisions in the absence of adequate telomerase (eg, 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 robust indicator of “biological age” (as opposed to just chronological age) and may represent a cumulative log of the number of cell divisions and a cumulative record of exposure to genotoxic and cytotoxic processes such as oxidation.^{7-9,113,131,132} Telomere length may also represent a biomarker for assessing an individual’s cumulative exposure to, or ability to cope with, depression or stressful conditions. For example, chronically stressed^{8,9} or depressed¹³³⁻¹³⁵ individuals show premature leukocyte telomere shortening, a sign of cellular aging. In the former study, telomere length was inversely correlated with perceived stress and with cumulative duration of caregiving stress.⁸ The estimated magnitude of the acceleration of biological aging in these studies was not trivial; it was estimated as approximately 9 to 17 additional years of chronological aging in the stressed caregivers and approximately 6 to 10 years in the depressed individuals. Preliminary data from our group suggest that telomere loss in MDD is most apparent in those individuals

with more chronic courses of depression,¹¹⁷ but another study did not observe that.¹³⁵ Interestingly, individuals with histories of early-life adversity or abuse also have shortened leukocyte telomeres.^{36,42,43} Since individuals with MDD are more likely to have experienced early-life adversity, it remains to be determined how much of the telomere shortening seen in studies of MDD relate to the MDD per se vs the histories of early-life adversity. In individuals with post-traumatic stress disorder (PTSD), telomere shortening was more closely linked to adverse childhood events than to the PTSD per se.⁴⁴

The importance of accelerated telomere shortening for understanding comorbid medical illnesses and premature mortality in depressed individuals is highlighted by multiple studies in nondepressed populations showing significantly increased medical morbidity and earlier mortality in those with shortened telomeres.^{7,136} For example, shortened leukocyte telomeres are associated with a greater than 3-fold increase in the risk of myocardial infarction and stroke and with a greater than 8-fold increase in the risk of death from infectious disease.¹³⁷ Thus, cell aging (as manifest by shortened telomeres), may provide a conceptual link between depression and its associated medical comorbidities and shortened life span.^{7,104,132} The causes of accelerated telomere loss in MDD are not known, but they may include chronic exposure to inflammation and oxidation, both of which are commonly seen in MDD and both of which are associated with telomere shortening. In our own studies, telomere length in MDD was inversely correlated with inflammation (IL-6 concentrations) and oxidative stress (the F2-isoprostane/ Vitamin C ratio).¹¹⁷

Telomere length is determined by the balance between telomere shortening stimuli (eg, mitotic divisions and exposure to inflammation and oxidation) and telomere lengthening or reparative stimuli. A major enzyme responsible for protecting, repairing, and lengthening telomeres is telomerase, a ribonucleoprotein enzyme that elongates telomeres, thereby counteracting telomere shortening and maintaining cellular viability.¹³¹ Telomerase may also have 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 (eg, ref 128). In one study in which telomere shortening was observed, telomerase activity

was significantly diminished in stressed (generally non-depressed) caregivers⁸ but, in another caregiver study (in which caregivers were more depressed than controls), telomerase activity was significantly increased.¹³⁸ We recently found that telomerase activity was significantly increased in unmedicated depressed individuals.¹³⁹ It is possible that increased telomerase activity, in the face of shortened telomeres, is an attempted compensatory response to telomere shortening.^{138,139}

Pointing to the inter-relatedness of several of the mediators considered in this review, telomerase activity can be down-regulated by cortisol,¹⁴⁰ tumor necrosis factor (TNF)- α and certain growth factors, and upregulated by IL-6 and certain other inflammatory cytokines, insulin-like growth factor-1, fibroblast growth factor-2, vascular endothelial growth factor, estrogen, and others.¹⁴¹

Novel treatment implications

To the extent the biochemical mediators we have described are pathophysiologically involved in MDD and its medical comorbidities, new classes of treatments should be considered, and certain noncanonical mechanisms of action of traditional antidepressants should be emphasized in new drug development. Some of these novel approaches are already under investigation, while others remain to be tested. In *Table II*, we list certain traditional and nontraditional, but mechanism-based, interventions that may ameliorate the biochemical mediators we have discussed. These interventions range from purely behavioral (eg, exercise and improved fitness, environmental enrichment, yoga and meditation, dietary macronutrient modifications and calorie restriction) (see refs 7,142-144 for description of these behavioral approaches) to more purely medication-based (see ref 145 for additional descriptions of novel biological mechanism-based therapeutics). For example, early work suggests the promise, at least in certain patients, of antiglucocorticoids,⁶⁷⁻⁶⁹ DHEA supplementation,¹⁷ insulin receptor sensitizers,^{99,146} glutamate antagonists,¹⁴⁷ calcium blockers,¹⁴⁸ anti-inflammatories,¹⁴⁹ antioxidants,¹⁵⁰ increased BDNF delivery to the brain,^{124,151} and, most speculatively, telomerase enhancers.^{152,153}

Summary: is depression accompanied by accelerated aging?

We began this review article by noting that depressed individuals are at increased risk of developing physical

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illnesses more commonly seen with aging. It remains unknown whether MDD and these medical conditions are causally related. This determination will be important in considering whether primary treatment of the depression (eg, with antidepressant medications or psychotherapy) should additionally treat some of the medical comorbidities (and vice versa) or whether the biochemical mediators that are common to both conditions (eg, inflammation and oxidation) should be a primary treatment focus. We also discussed the potent influence that early-life adversity can have on the subsequent development of depression and medical comorbidities. We noted that many of the biochemical mediators are linked to others, and that there are many examples of bidirectional influence. Finally, we postulated that certain of these mediators have the potential to accelerate cellular aging at the level of DNA. In any event, is important to recognize that MDD may be biologically heterogeneous, and this model may apply only to certain subsets of patients with MDD. This reconceptualization

of MDD as a constellation of biochemical features conducive to physical as well as mental distress places MDD firmly in the taxonomy of physical disease and points to new types of treatment. □

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Biochemical mediator	Potential treatment interventions
Stress vulnerability	Stress reduction; meditation; lifestyle changes ^{7,142,154}
Epigenetic changes	Epigenetic reprogramming ^{155,156}
LHPA axis dysregulation (Hypercortisolemia + GC resistance)	Antidepressants upregulate GR function ⁷¹ CRH antagonists ¹⁵⁷ Cortisol antagonists and GR antagonists or agonists ⁶⁶⁻⁶⁹
Glucose/insulin dysregulation	Insulin receptor sensitizers ^{99,146}
Glutamate/excitotoxicity	Glutamate antagonists ¹⁴⁷
Oxidative stress	Antidepressants have antioxidant effects ¹²⁰ Antioxidants ^{150,158}
Intracellular calcium	Calcium blockers ¹⁴⁸
Inflammation	Antidepressants have anti-inflammatory effects ²⁰ Anti-inflammatory drugs, TNF- α antagonists, etc ¹⁴⁹
Decreased counter-regulatory neurosteroids	SSRIs increase allopregnanolone synthesis ^{77,78} DHEA administration ¹⁷
Decreased BDNF	Antidepressants (esp SSRIs) increase BDNF concentrations ^{122,123} Environmental enrichment ^{143,144} Exercise ¹⁴³ Dietary restriction ¹⁴³ BDNF administration via novel routes or vectors ^{124,151}
Cell aging (telomeres; telomerase)	Telomerase activation ^{152,153}

Table II. Potential mechanism-based therapeutic interventions. LHPA, limbic-hypothalamic-pituitary-adrenal; GC, glucocorticoid; GR, glucocorticoid receptor; CRH, corticotrophin-releasing hormone; DHEA, dehydroepiandrosterone; BDNF brain-derived neurotrophic factor; TNF, tumor necrosis factor; SSRI, selective serotonin reuptake inhibitor

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Translational research

Sanidad del cuerpo y del espíritu: depresión, enfermedad y envejecimiento acelerado

El trastorno depresivo mayor (TDM) tiene una alta frecuencia de asociación con el desarrollo de importantes comorbilidades médicas como enfermedad cardiovascular, accidentes vasculares, demencia, osteoporosis, diabetes y síndrome metabólico. Estas son patologías que de preferencia ocurren en la edad tardía de la vida y se ha propuesto que el TDM puede estar asociado con un “envejecimiento acelerado”. Se revisan algunos moderadores y mediadores que pueden acompañar al TDM y dar origen a estas condiciones médicas comórbidas. En primer lugar se revisan los efectos moderadores de los estilos psicológicos de adaptación, de la predisposición genética y de las modificaciones epigenéticas (por ejemplo, secundarias a la adversidad infantil). A continuación se revisan algunos mediadores interrelacionados que se presentan en el TDM (o al menos en algunos subtipos de TDM) que pueden incidir en la comorbilidad médica y en el envejecimiento acelerado: alteraciones del eje límbico-hipotalámico-hipofisiario-adrenal, disminución de la función de los receptores de glucocorticoides, alteraciones en la tolerancia a la glucosa y en la sensibilidad a la insulina, excitotoxicidad, aumento del calcio intracelular, estrés oxidativo, un ambiente proinflamatorio, reducción de los niveles de neuroesteroides “contra-reguladores” (como alopregnanolona y dehidroepiandrosterona), disminución de la actividad neurotrófica y un envejecimiento celular acelerado que se manifiesta en alteraciones de la actividad de la telomerasa y acortamiento de los telómeros, lo que puede llevar a la apoptosis y la muerte celular. En este modelo, el TDM está caracterizado por un exceso de mediadores potencialmente destructores y una insuficiencia de los protectores o restauradores. Estos factores interactúan aumentando la posibilidad de enfermedad física y de un envejecimiento acelerado a nivel celular. Se concluye con propuestas de nuevas terapias basadas en los mecanismos que regulan estos mediadores.

Sain de corps et d'esprit : dépression, maladie et vieillissement accéléré

Le trouble dépressif majeur (TDM) est associé à un taux élevé de comorbidités graves comme les pathologies cardiovasculaires, les accidents vasculaires cérébraux (AVC), la démence, l'ostéoporose, le diabète et le syndrome métabolique. Ces pathologies surviennent habituellement tard dans la vie, et c'est pourquoi certains ont suggéré que le TDM pourrait être associé à un « vieillissement accéléré ». Dans cette revue, nous analysons plusieurs modérateurs et médiateurs pouvant accompagner le TDM et susceptibles de précipiter ces comorbidités. Tout d'abord, nous passons en revue les effets modérateurs des stratégies psychologiques d'adaptation (coping), des prédispositions génétiques et des modifications épigénétiques (par ex secondaires à des difficultés dans l'enfance). Nous nous consacrons ensuite à plusieurs médiateurs liés entre eux intervenant dans le TDM (ou au moins dans certains sous-types de TDM) qui pourraient contribuer à la charge comorbide et à l'accélération du vieillissement : modifications de l'axe limbo-hypophyso-hypothalamo-surrénalien, diminution de la fonction du récepteur des glucocorticoides, modification de la tolérance au glucose et de la sensibilité à l'insuline, excitotoxicité, augmentation du calcium intracellulaire, stress oxydatif, un milieu pro-inflammatoire, abaissement des taux des neurostéroïdes « contre-régulateurs » (comme l'allopregnanolone et la déhydroépiandrosterone), diminution de l'activité neurotrophique et accélération du vieillissement cellulaire, se manifestant par des modifications de l'activité de la télomérase et par un raccourcissement des télomères, pouvant conduire à l'apoptose et à la mort cellulaire. Dans ce modèle, le TDM se caractérise par un excès de médiateurs potentiellement destructeurs et par une insuffisance de médiateurs protecteurs et restaurateurs. Ces facteurs interagissent en augmentant la probabilité de pathologie physique et de vieillissement accéléré à un niveau cellulaire. Nous concluons avec des suggestions concernant de mécanismes nouveaux pour des traitements s'appuyant sur ces médiateurs.

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