

## EXPERT REVIEW

## The organization of the stress system and its dysregulation in depressive illness

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Stressors are imminent or perceived challenges to homeostasis. The stress response is an innate, stereotypic, adaptive response to stressors that has evolved in the service of restoring the nonstressed homeostatic set point. It is encoded in specific neuroanatomical sites that activate a specific repertoire of cognitive, behavioral and physiologic phenomena. Adaptive responses, though essential for survival, can become dysregulated and result in disease. A clear example is autoimmune disease. I postulate that depression, like autoimmunity, represents a dysregulated adaptive response: a stress response that has gone awry. The cardinal manifestation of the normal stress response is anxiety. Cognitive programs shift from complex associative operations to rapid retrieval of unconscious emotional memories acquired during prior threatening situations. These emerge automatically to promote survival. To prevent distraction during stressful situations, the capacity to seek and experience pleasure is reduced, food intake is diminished and sexual activity and sleep are held in abeyance. Monoamines, cytokines, glutamate, GABA and other central mediators have key roles in the normal stress response. Many central loci are involved. The subgenual prefrontal cortex restrains the amygdala, the corticotropin-releasing hormone/hypothalamic–pituitary–adrenal (CRH/HPA) axis and the sympathomedullary system. The function of the subgenual prefrontal cortex is moderately diminished during normal stress to disinhibit these loci. This disinhibition promotes anxiety and physiological hyperarousal, while diminishing appetite and sleep. The dorsolateral prefrontal cortex is downregulated, diminishing cognitive regulation of anxiety. The nucleus accumbens is also downregulated, to reduce the propensity for distraction by pleasurable stimuli or the capacity to experience pleasure. Insulin resistance, inflammation and a prothrombotic state acutely emerge. These provide increased glucose for the brain and establish premonitory, proinflammatory and prothrombotic states in anticipation of either injury or hemorrhage during a threatening situation. Essential adaptive intracellular changes include increased neurogenesis, enhancement of neuroplasticity and deployment of a successful endoplasmic reticulum stress response. In melancholic depression, the activities of the central glutamate, norepinephrine and central cytokine systems are significantly and persistently increased. The subgenual prefrontal cortex is functionally impaired, and its size is reduced by as much as 40%. This leads to sustained anxiety and activations of the amygdala, CRH/HPA axis, the sympathomedullary system and their sequella, including early morning awakening and loss of appetite. The sustained activation of the amygdala, in turn, further activates stress system neuroendocrine and autonomic functions. The activity of the nucleus accumbens is further decreased and anhedonia emerges. Concomitantly, neurogenesis and neuroplasticity fall significantly. Antidepressants ameliorate many of these processes. The processes that lead to the behavioral and physiological manifestations of depressive illness produce a significant decrease in lifespan, and a doubling of the incidence of premature coronary artery disease. The incidences of premature diabetes and osteoporosis are also substantially increased. Six physiological processes that occur during stress and that are markedly increased in melancholia set into motion six different mechanisms to produce inflammation, as well as sustained insulin resistance and a prothrombotic state. Clinically, melancholic and atypical depression seem to be antithesis of one another. In melancholia, depressive systems are at their worst in the morning when arousal systems, such as the CRH/HPA axis and the noradrenergic systems, are at their maxima. In atypical depression, depressive symptoms are at their worst in the evening, when these arousal systems are at their minima. Melancholic patients experience anorexia and insomnia, whereas atypical patients experience hyperphagia and hypersomnia. Melancholia seems like an activation and persistence of the normal stress response, whereas atypical depression resembles a stress response that has been excessively inhibited. It is important that we stratify clinical studies of depressed patients to compare melancholic and atypical subtypes and establish their differential pathophysiology. Overall, it is important to note that many of the major mediators of the stress response and melancholic depression, such as the subgenual prefrontal cortex, the amygdala, the noradrenergic system and the CRH/HPA axis participate in multiple reinforcing positive feedback loops. This organization permits the establishment of the markedly exaggerated, persistent elevation of the stress response seen in melancholia. Given their pronounced interrelatedness, it may not matter where in this cascade the first abnormality arises. It will spread to the other loci and initiate each of their activations in a pernicious vicious cycle.

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## INTRODUCTION

Over 2000 years ago, Hippocrates wrote that the most catastrophic illnesses occurred in the context of an increase in 'black bile', one of four 'humors' that dominated medical thinking at the time. Black bile was the most ominous of the humors. In Greek, black bile is represented by the words *melan chole*, the root of our word melancholy, denoting a great sorrow. Accordingly, black bile was associated with two of mankind's most dreaded scourges, cancer and depression, no less than a cancer of the self that devours without always killing.

## THE NORMAL STRESS RESPONSE

### Overview

Hippocrates wrote that we are all beset by disturbing forces that upset our balance. Fortunately, there were forces at work that helped restore balance that Galen referred to as *vis medicatrix naturae*, the healing forces of nature. Today we call the disturbing forces stressors, the healing forces of nature, adaptive responses, and the balance, homeostasis. In this context, stressors can be seen as imminent or perceived challenges to homeostasis. The stress response is an innate, relatively stereotypic adaptive response that has evolved to further perturb homeostatic controls in the service of restoring the normal, nonstressed homeostatic set point. Stress is almost always accompanied by arousal and is most robust when the stimulus is seen as aversive and uncontrollable. Like other adaptive responses, such as the immune response, the stress response is essential for survival.<sup>1–3</sup>

Centuries after Hippocrates, Sydenham noted that a dysregulated adaptive response could also act to further destabilize our homeostasis. Autoimmune disease is an example of a disturbed adaptive response. I postulate here that depression represents another form of a dysregulated adaptive response, a stress response that has gone awry.

When we are not stressed, the extensive projections of the prefrontal cortex coordinate the brain's activity for effective regulation of behavior, thought and emotion.<sup>4</sup> Anxiety is well managed by prefrontal loci, euthymia is the prevailing mood and cognition is relatively unfettered by anxiety. When we are stressed, the brain transitions to the more rapid emotional responses of the amygdala and related limbic structures.<sup>4</sup> This paper will review the healthy organization of the stress system and the extent to which depressive illness reflects a dysregulation of this critical adaptive function.

## HEALTHY BEHAVIORAL AND PHYSIOLOGICAL RESPONSES DURING STRESS: A PRELUDE TO DEPRESSION

During stress, anxiety is essential for survival. Attention is focused predominantly on the threatening stressor. Cognitive function is shifted away from complex, associative programs to those that are often stored unconsciously that can emerge virtually automatically. This shift provides an immediate answer to the stress at hand.<sup>5</sup> Dysphoria is limited during stress so that an effective stress response can be mounted.

Physiologically, the hypothalamic–pituitary–adrenal (HPA) axis, the locus ceruleus norepinephrine system and the adrenal medulla are activated virtually simultaneously. In addition, insulin resistance,<sup>6</sup> mild inflammation<sup>7</sup> and a prothrombotic state<sup>6</sup> emerge reflexively to provide glucose for the brain, and for premonitory readiness for expected injuries or hemorrhage during fight-or-flight situations. To preserve calories for the stress response, the growth hormone, gonadal and thyroid axes are partially inhibited at both central and peripheral loci.

Essential adaptive intracellular changes during the normal stress response include neurogenesis,<sup>8</sup> enhancement of neural plasticity<sup>9</sup> and a successful endoplasmic reticulum stress response

(please see below).<sup>10,11</sup> These phenomena provide new neurons, promote dendritic growth, new synapses, and facilitate effective protein folding in the face of increased demand for neuronal protein synthesis. In addition, a successful stress response requires continuity of the response until it is no longer needed.

One feature of the stress system is the presence of multiple, redundant positive feedback mechanisms among many stress system components, which, if unchecked, can lead to pathological states. Evolution has built the stress system so, that if necessary, it can respond very forcefully. This feature also sows the seeds of multiple dysregulations in stress system activity that can lead to illness.

## FOUR SPECIFIC COMPONENTS OF THE NORMAL STRESS RESPONSE AND THEIR DYSREGULATION IN DEPRESSION

I will discuss the important components of the normal stress response and, in parallel, their dysregulations in depressive illness. The following four components of the stress response will serve as organizing features for the remainder of this review:

1. Behavioral responses: (A) establishing a state of mild anxiety; (B) shifts in attention and cognition; (C) dysphoria; (D) altered pleasure and reward processing.
2. Metabolic, hormonal and neurotransmitter responses: (A) corticotropin-releasing hormone (CRH)/HPA axis activation, including cortisol; (B) activation of the locus ceruleus norepinephrine and the sympathetic nervous systems; (C) monoaminergic neurotransmitters; (D) the glutamate system (including ketamine in depression); (E) inflammation, insulin resistance and a prothrombotic state.
3. Promotion of neuronal integrity during the extra demands of responding to stressors: (A) brain-derived neurotrophic factor (BDNF) (B) neuroplasticity; (C) neurogenesis; (D) the endoplasmic reticulum stress response; (E) adaptive epigenetic phenomena.
4. Appropriately sustaining the stress response: (A) mechanisms to insure the continuity of the stress response until it is no longer needed.

## REGULATION OF THE VARIOUS COMPONENTS OF THE NORMAL STRESS RESPONSE

### 1. Behavioral responses

*A. Establishing a state of mild anxiety during the normal stress response.* The subgenual prefrontal cortex has a major role in managing anxiety by restraining the amygdala and promoting the extinction of conscious or unconscious aversively charged emotional memories. Psychological stressors in healthy controls, such as anticipatory anxiety, downregulate the normal functions of the subgenual prefrontal cortex. As a consequence, the amygdala is activated and anxiety ensues, so that the stress response can emerge.<sup>12</sup>

During anxiety secondary to interpersonal stress, the subgenual prefrontal cortex is first downregulated and a disinhibited amygdala emerges to promote anxiety. In response to a physical stressor, stimuli from below activate the amygdala first, and the amygdala then inhibits the subgenual prefrontal cortex.

A vicious, reverberatory cycle may potentially occur between the subgenual prefrontal cortex and the amygdala. Thus, if the subgenual prefrontal cortex is downregulated, the amygdala is activated, which further inhibits the subgenual prefrontal cortex. A subgenual cortex that is further inhibited leads to further activation of the amygdala. This cycle, if unregulated, can lead to depression (please see below).

Among its many functions, the subgenual prefrontal cortex also helps in the accurate estimation of the likelihood of punishment

and reward. An estimate of the likelihood of punishment also increases anxiety. The subgenual prefrontal cortex has many other roles that will emerge in the subsequent discussion.<sup>13</sup>

Although the subgenual prefrontal cortex regulates emotional control over anxiety, the dorsolateral prefrontal cortex exerts cognitive control over fear-related thoughts and behaviors. It is also an important site for working memory, and aids in complex sequence-dependent cognitive operations. These functions of the dorsolateral prefrontal cortex are also downregulated during stress.<sup>4</sup>

In addition to the subgenual and dorsolateral prefrontal cortices, the amygdala restrains other prefrontal cortical sites and modulates numerous limbic, striatal, hypothalamic, brain stem and autonomic centers that are activated in response to stressors. As an example, the amygdala is a potent stimulus to the HPA axis, locus ceruleus–norepinephrine system and the sympathetic nervous system.

*B. Adaptive alterations in attention and memory function that promote a successful stress response.* The anxiety that emerges during the stress response biases attention towards the threatening stimulus and away from less critical stimuli. Moreover, the capacity for attentional disengagement from the threatening stimulus is diminished until the stress has passed. This feature reflects, in part, a slightly decreased activity of the ventrolateral prefrontal cortex, which assists in facilitating changes in set. Multiple brain sites participate in attention. Their functions and interactions will be covered in more detail in the depression section.

Emotional memories are very well remembered, and many are stored unconsciously in the amygdala and hippocampus. They can emerge unconsciously in the context of exposure to a situation or place that had activated the stress system years before. Cortisol and norepinephrine secretion during stress both promote the retrieval of these emotional memories and aid in their further consolidation.<sup>5</sup> A burden of many aversive emotional memories acquired over a lifetime, stored in sites like the amygdala and the hippocampus, predisposes to stress-related illnesses, including depression.

The inhibition of the dorsolateral prefrontal cortex leads to a modest decrease in working memory.<sup>4</sup> There is preferential access to previously stored emotional memories in the amygdala that facilitate adaptation to the current threat.

In contrast to the role of facilitating the encoding of aversively charged memory in the hippocampus, cortisol causes a decrease in hippocampal-mediated declarative memory. The hippocampus has an important role in the regulation of cortisol secretion. The activity of the HPA axis is restrained via activation of the type 2 glucocorticoid receptor in the hippocampus. This feedback loop is blunted during acute stress.<sup>1–3</sup>

The anterior hippocampus is connected directly to the subgenual prefrontal cortex. Appropriate metabolic activity of the anterior hippocampus promotes the nonstressed state of the subgenual prefrontal cortex. Increased metabolic activity of the anterior hippocampus promotes an increase in the metabolic activity in the subgenual prefrontal cortex, which is the stressed state of this structure, resulting in increased anxiety.<sup>14</sup>

*C. Limiting dysphoria during the normal stress response.* The subgenual prefrontal cortex has a particularly important role in the experience and/or regulation of dysphoric emotion.<sup>13</sup> In healthy volunteers, the metabolic activity of the subgenual prefrontal cortex increases and its functions, such as restraining anxiety, decrease during sadness induction and exposure to traumatic reminders.<sup>13</sup> The subgenual cortex also has a highly significant role in self-referential attribution and self-appraisal.<sup>13,15</sup> The nonstressed functions of the subgenual prefrontal cortex are only moderately suppressed during a normally functioning stress response. In contrast to the substantial hypercortisolism of prolonged, severe stress, modest cortisol secretion during acute stress

increases nucleus accumbens activity. Overall, the nucleus accumbens is only moderately downregulated during acute stress. Thus, the stressed individual retains sufficient morale to execute a healthy stress response.

*D. Altered pleasure and reward processing during the normal stress response.* The capacity to experience pleasure is reduced during stress, partly to diminish the likelihood of distraction during the stress response. The nucleus accumbens has an important role in modulating pleasure and reward and receives a rich supply of dopaminergic input from ventral tegmental area dopaminergic neurons in the brain stem.<sup>16</sup> As noted, the overall activity of the nucleus accumbens is only moderately reduced during stress.

The subgenual prefrontal cortex has an important role in modulating the nucleus accumbens. It sends and receives many fibers from brain stem ventral tegmental area dopaminergic neurons. When the subgenual prefrontal cortex is appropriately functioning, ventral tegmental area neurons increase dopamine release in the nucleus accumbens. Decreased functionality of the subgenual prefrontal cortex impairs reward-learning processes.<sup>13,15</sup>

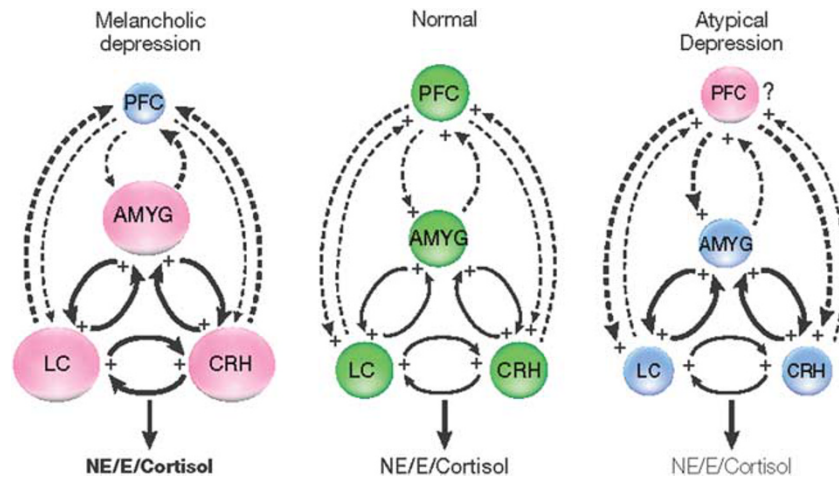
Humans with lesions of the subgenual prefrontal cortex have a relative inability to use information regarding the likelihood of punishment versus reward in guiding social behavior.<sup>13,15</sup> The orbital prefrontal cortex is responsible for the appropriate use of information regarding reward and pleasure to guide the choice of behaviors during shifting environmental circumstances. Its activity is also moderately reduced during stress.<sup>15</sup>

## 2. Metabolic, hormonal and neurotransmitter factors during acute stress

*A. Activation of the CRH/HPA axis that contribute to a successful stress response.* The subgenual prefrontal cortex is the only cortical site that sends direct projections to the hypothalamus.<sup>17</sup> It exerts cortical-mediated inhibition upon the CRH/HPA axis and the sympathetic nervous system.<sup>17</sup> A moderately suppressed subgenual prefrontal cortex during stress leads to a moderate disinhibition of the CRH and sympathetic nervous systems, and leads to the secretion of cortisol and norepinephrine. An activated amygdala during stress also stimulates the CRH/HPA axis and sympathetic nervous system.<sup>18</sup>

In addition to activating the HPA axis, CRH has many additional roles during the normal stress response. CRH is located in the amygdala, the hypothalamus and in sympathetic nerve terminals. CRH directly promotes anxiety and fear-related behaviors.<sup>19</sup> It activates the locus ceruleus to promote arousal and an improved signal-to-noise relationship among the components of the stress response.<sup>20</sup> It activates the sympathomedullary system for the secretion of norepinephrine and epinephrine.<sup>21</sup> On the other hand, CRH inhibits the thyroid, gonadal and growth hormone axes to preserve calories for responding to the immediate stressor. In addition, CRH inhibits appetite and sleep.<sup>1–3</sup> CRH released from sympathetic nerve terminals activates the innate immune response.<sup>22</sup> As an example, CRH is a potent stimulus for the degranulation of mast cells.

Cortisol has many key roles in the stress response, which cannot proceed in the face of profound glucocorticoid deficiency. Cortisol activates the amygdala to promote anxiety, arousal and conditioned fear responses.<sup>23</sup> Cortisol increases cardiac contractility and the sensitivity of noradrenergic beta-receptors. By promoting mild, brief insulin resistance, cortisol helps mobilize glucose for the brain and stressed body sites. Cortisol also activates the renin-angiotensin and endothelin systems for premonitory protection from loss of blood pressure secondary to possible blood loss during a fight-or-flight situation. In addition to CRH acting centrally, cortisol directly downregulates the thyroid, gonadal and growth hormone axes in the periphery.



**Figure 1.** Multiple reinforcing positive feedback loops among the subgenual prefrontal cortex, amygdala, locus ceruleus–NE system and hypothalamus. Solid lines refer to stimulatory effects, dotted lines to inhibitory ones. Melancholic depression, the normal resting state and atypical depression are shown in this figure. (1) The subgenual prefrontal cortex restrains the amygdala and the amygdala restrains the subgenual prefrontal cortex. If the subgenual prefrontal cortex becomes hypoactive, the amygdala activity increases and further restrains the subgenual prefrontal cortex. (2) The amygdala stimulates the locus ceruleus–norepinephrine system and the CRH/HPA axis. These, in turn, stimulate the amygdala and another positive feedback loop is initiated. The amygdala activity further restrains the subgenual prefrontal cortex. (3) An activated locus ceruleus–norepinephrine system and CRH/HPA axis both inhibit the subgenual prefrontal cortex, further exacerbating multiple other positive feedback loops. (4) The locus ceruleus–norepinephrine system and the CRH/HPA axis stimulate one another. They activate the amygdala and inhibit the subgenual prefrontal cortex. These multiple feedback loops highlight the extent to which evolution has invested in being able to generate an extremely powerful stress response. AMYG, amygdala; CRH/HPA, corticotropin-releasing hormone/hypothalamic–pituitary–adrenal; E, epinephrine; LC, locus ceruleus; NE, norepinephrine; PFC, prefrontal cortex.

The CRH/HPA axis participates in several positive feedback loops with other mediators of the stress response including the noradrenergic system and the amygdala (please see Figure 1). This figure highlights many of the redundant positive feedback loops operating within the stress system.

**B. Activation of the locus ceruleus and the sympathetic nervous system that contributes towards a successful stress response.** The locus ceruleus is the key site for the norepinephrine system in brain and sends millions of nerve terminals to the cortex and almost all the other areas of the brain. Locus ceruleus norepinephrine serves globally as an emergency or alarm system leading to decreases in neurovegetative functions, such as eating or sleeping, and at the same time, fine tunes the signal-to-noise ratio among the neurons of the stress system.<sup>20</sup> Norepinephrine contributes to accompanying increases in autonomic and neuroendocrine responses to stress, including the CRH/HPA axis.

Another function of norepinephrine during the stress response is to directly activate the amygdala and to inhibit the medial prefrontal cortex, including the subgenual prefrontal cortex.<sup>18</sup> In addition, as noted norepinephrine enhances the long-term storage and retrieval of aversively charged emotional memories in sites such as the hippocampus, amygdala and striatum.<sup>5</sup>

Sympathetic neurons are frequently considered to be a part of the peripheral nervous system, although there are many that lie within the central nervous system. Activation of the sympathetic nervous system leads to pupillary dilatation, increases in the rate and forcefulness of cardiac contraction, dilatation of bronchioles, dilatation of blood vessels in skeletal muscle and constriction of blood vessels in the gastrointestinal tract. It also inhibits peristalsis in the gastrointestinal tract and increases renin secretion by the kidney. All of these promote survival during a fight-or-flight situation.

The central noradrenergic system and the sympathetic nervous system participate in several positive feedback effects including ones with the CRH/HPA axis, the amygdala and the prefrontal cortex (please see Figure 1).

**C. Monoaminergic neurotransmitters during the normal stress response.** Many reviews of monoaminergic neurotransmitters in depression have appeared in the literature, and an extensive discussion is beyond the scope of this review. The role of norepinephrine in the normal stress response has been briefly alluded to above. The impact of reserpine treatment in the precipitation of depression is likely to represent dopaminergic depletion, as norepinephrine secretion is increased in melancholic depression.<sup>24</sup>

Dopaminergic activity is moderately reduced during stress. Ordinarily, serotonin reduces the metabolic activity of the subgenual prefrontal cortex, resulting in this key structure being in the nonstressed state. Conversely, a decrement in serotonin neurotransmission and a deficient activation of postsynaptic 5HT-1a receptors increases the metabolic activity of the subgenual prefrontal cortex, thus promoting the stressed state. Similarly, serotonin decreases the firing rate of the amygdala.<sup>25</sup>

**D. Activity of the glutamate system during the normal stress response.** Glutamate is the most plentiful neurotransmitter in the brain and is present in more than 50% of the synapses in the CNS. It is highly excitatory, increasing the firing rate of neurons that promote adaptive responses to stressful situations, including the CRH, locus ceruleus–norepinephrine and sympathetic nervous systems. During a normal stress response, appropriate glutamate activity also promotes adaptive neurogenesis and neuroplasticity. When glutamate activity is excessive, excitotoxicity can occur, leading to cellular damage or apoptosis, disturbances in dendritic architecture and a reduction in stress-induced neurogenesis (see below).<sup>26</sup>

**E. Inflammation, insulin resistance and a prothrombotic state during the normal stress response.** As noted, a proinflammatory state, documented by the secretion of a host of inflammatory mediators, is an inherent component of the normal stress response.<sup>7</sup> The response occurs, in part, to provide a premonitory reading of



the immune response in case of injury during a fight-or-flight situation.

Insulin resistance leads to a rise in plasma glucose,<sup>6</sup> which is essential for stressed body sites and the brain, which runs the stress response and needs extra energy. In addition, the hippocampus, the immune system and the breast do not require insulin for the transport of glucose into the cell. They are protected from glucoprivation during the stress response.

A prothrombotic state also occurs routinely during the normal stress response.<sup>5</sup> This occurs as a premonitory defense against possible hemorrhage during an injury incurred during the stress response.

The release of cytokines during the peripheral stress response is particularly important, and, beyond their roles in inflammation, they are extremely potent reinforcers of many components of the peripheral stress response. Specifically, at extremely low concentrations, cytokines activate the CRH system and the HPA axis,<sup>27</sup> the sympathetic nervous system,<sup>28</sup> promote insulin resistance,<sup>29</sup> and activate multiple components of the coagulation system.<sup>30</sup> They also stimulate the acute-phase response, consisting of a group of over 20 compounds that exert multiple proinflammatory and prothrombotic effects relevant to the stress response.<sup>31,32</sup>

In addition to their manifold peripheral effects, cytokines have pleiotropic effects on the central nervous system. They not only influence inflammation centrally, but also have key roles in neurotransmitter function, neuroendocrine regulation, neuroplasticity and neurotrophic support.<sup>33</sup> (Please see below in the section on depression for a more detailed discussion.)

The mediators of the inflammatory response participate in several positive feedback loops that include the noradrenergic system, the HPA axis and the insulin receptor system.

### 3. Promotion of neuronal integrity during the extra demands of responding to stressors

**A. Brain-derived neurotrophic factor.** BDNF has many key roles in CNS function of relevance to well-being, a successful stress response and the pathophysiology of depression.<sup>34</sup> It is intimately involved in the development of neural circuits at many stages. These include neurogenesis and neural stem cell survival and differentiation, axon/dendrite differentiation, growth and guidance of axons, synapse formation and maturation and refinement of developing circuits.<sup>35</sup>

Direct infusion of BDNF into the dentate gyrus zone of the hippocampus or subventricular zone increases the number of adult-born neurons. BDNF also acts to regulate the survival and differentiation of neural stem cells.<sup>34</sup>

With respect to neural circuit development, deletion of BDNF in mice inhibits the differentiation of interneurons. Conditional BDNF knockout showed that the absence of BDNF did not lead to a reduction in neuronal number. It did lead, however, to a region-specific reduction in dendritic complexity and spine density. The findings indicate that BDNF is not a survival factor for neurons, but rather a differentiation factor.<sup>34–36</sup>

Mild controllable stress, such as voluntary exercise, increases the activities of BDNF at multiple levels and may contribute to the reported salutary effects of exercise on the stigmata of depressive illness. Positive experiences, such as early nurturing, also potentiate BDNF activity. On the other hand, sustained and uncontrollable stress significantly diminishes many of BDNF's salutary effects in the CNS and produces, instead, potentiation of anxiety. While chronic stress decreases the hippocampal expression of BDNF, it increases the expression of BDNF in the amygdala and promotes dendritic branching. As prolonged, aversive and uncontrollable stress is a significant risk factor for depressive illness, this may, in part, contribute to the development of stress-related depressive illness.<sup>8,34,35,37</sup>

Many BDNF effects, such as its role in neurogenesis, neural stem cell survival and differentiation, neuronal differentiation, effects on glutaminergic neurotransmission and increased translation of mTOR, bear directly on pathophysiological mechanisms that have a role in depressive disorders and in processes that promote recovery from depression.<sup>34,35,38</sup>

**B. The role of neuronal neuroplasticity during the normal stress response.** The complexity of neuronal dendrites and the number of spinal synapses increase during mild controllable stress to promote new connections among neurons. The formation of spinal synapses, termed synaptogenesis, is a key form of neuroplasticity. This neuroplasticity represents a basic characteristic of neurons. It is a structural change that occurs whenever there is synaptic activity. It provides the means for processing and including new information that can be used to make appropriate responses to a changing environment.<sup>9</sup>

**C. The role of neurogenesis during the normal stress response.** We now know that the adult brain is capable of neurogenesis in the dentate gyrus of the hippocampus.<sup>8,39</sup> Neurogenesis occurring in adults show heightened synaptic plasticity during their maturation and can account for as much as 10% of the entire dentate gyrus granule cell population.<sup>40</sup> Neurogenesis also occurs in the subgranular zone of the lateral ventricles.

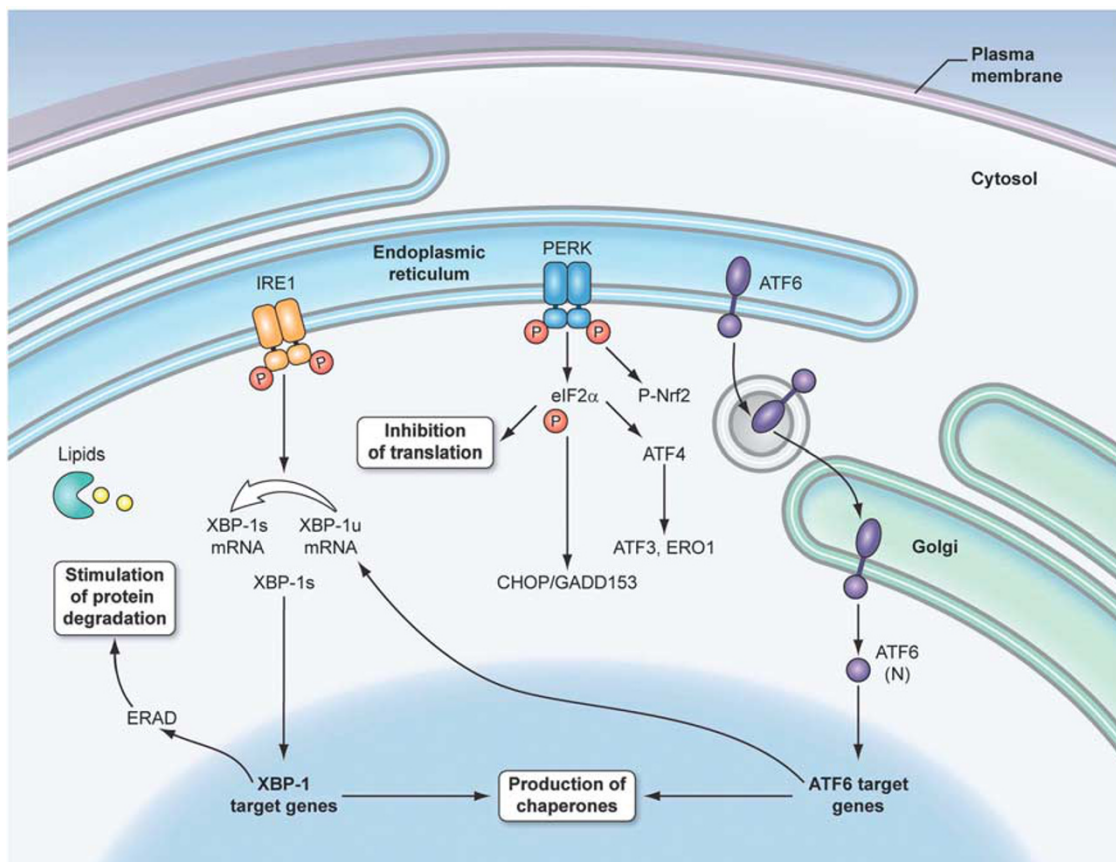
Several stimuli are known to stimulate neurogenesis in the dentate gyrus. These include interventions associated with the beneficial effects on cognition and mood such as learning, environmental richness, exercise and prolonged treatment with antidepressants. Acute, mild, controllable stress also induces neurogenesis in the dentate gyrus.<sup>8,39</sup>

Recent data indicate that neurogenesis is associated with a specific form of learning, consisting of an improved efficiency in the differentiation between overlapping contextual representations. This capacity is indicative of enhanced pattern recognition. Pattern recognition may be important for remembering and identifying harmful signals or dangerous situations. Thus, neurogenesis promotes recognizing stressors that are threatening.<sup>40</sup>

The production of adult-born neurons also helps buffer the brains of mice against stress. Without them, mice have abnormal stress responses represented, in part, by corticosterone responses that do not come back to baseline long after the stressor has been terminated. However, neurogenesis alone does not exert anxiolytic effects in nonstressed mice.<sup>41</sup>

Mice stressed for half an hour show no evidence of depression-like features. However, those in which neurogenesis had been impeded demonstrated several depression-like traits, including decreased exploration, learned helplessness and a loss of preference for sweet solutions over water. On the other hand, blocking neurogenesis *per se* did not promote depressive features.<sup>34</sup>

**D. The role of the cellular endoplasmic reticulum stress response during the normal stress response.** The endoplasmic reticulum stress response helps to maintain cellular integrity in the face of stressors such as glutamate-mediated excitotoxicity.<sup>10,11</sup> During highly intense stressful situations, the hypersecretion of glutamate and other compounds can result in the hyperexcitability of neurons and the demand for significantly more protein synthesis. Endoplasmic reticulum stress is the term given to an imbalance between cellular demand for endoplasmic reticulum function and endoplasmic reticulum capacity to effectively fold normal proteins.<sup>10,11</sup> If the endoplasmic reticulum stress response can fully resolve the problem, so that only normal proteins are produced, the cell survives. If residual unfolded proteins remain



**Figure 2.** Endoplasmic reticulum stress: function and relevance to depression. During highly intense stressful situations, the hypersecretion of glutamate and other compounds can result in the hyperexcitability of neurons and the demand for significantly more protein synthesis. Endoplasmic reticulum stress is the term given to an imbalance between cellular demand for endoplasmic reticulum function and endoplasmic reticulum capacity to effectively fold normal proteins. If the endoplasmic reticulum stress response can fully resolve the problem, so that only normal proteins are produced, the cell survives. If residual unfolded proteins remain that would be released as mutant proteins, a specific apoptotic response occurs. The endoplasmic reticulum (ER) stress response results in the production of chaperones that promote folding, activation of the endoplasmic reticulum-associated degradation (ERAD) program, which degrades proteins and inhibition of translation. These activities are signaled through three ER stress sensors: PERK, IR1a and ATF6. Patients with bipolar disorder have been reported to have a polymorphism in the XBP-1 gene, associated with decreased expression of XBP-1. Normally, XBP-1 is crucial to the activation of the ERAD program and increases in chaperones such as GRP 78. BDNF is a potent stimulus to XBP-1. Valproate exerts multiple effects to influence the ER response in favor of cell rescue. These effects occur, in part, via stimulation of the ATF6 branch of the ER stress response. ATF6 is the gene upstream of XBP-1 and is a potent stimulus to XBP-1 expression. Valproate also exerts a stimulatory effect on the production of chaperones and on the ERAD response independent of its effect on ATF6. Lithium also exerts multiple effects on the ER response in favor of cell rescue. Lithium promotes the expression of chaperones and Bcl-2. Both valproate and lithium inactivate glycogen synthase kinase 3 (GSK-3), which transduces many downstream effects that occur in the context of activation of the ER stress response, leading to apoptosis. Mutation of the WFS1 protein leads to Wolfram's Syndrome, which is associated with endoplasmic reticulum stress and a high incidence of serious affective illness (figure adapted from Hotamisligil). BDNF, brain-derived neurotrophic factor.

that would be released as mutant proteins, a specific apoptotic response occurs.

The endoplasmic reticulum stress response results in the production of chaperones that promote folding, activation of the endoplasmic reticulum-associated degradation (ERAD) program, which degrades proteins and inhibition of translation (Figure 2). These activities are signaled through three ER stress sensors: PERK, IR1a and ATF6 (Figure 2).<sup>10,11</sup>

*E. Epigenetic changes and the normal stress response: effects that promote a successful stress response.* Epigenetics involves genetic control by factors other than a change in an individual's DNA sequence. Epigenetic changes can switch genes on or off. This will determine which proteins are transcribed. Environmental events and behavioral experience induce epigenetic changes at

particular gene loci that help shape neuronal plasticity and function.<sup>42,43</sup>

Epigenetics is involved in many cellular processes. The many cells types that we have are largely determined by which genes are turned on or off. Epigenetic silencing is one way to turn genes on or off and it can contribute to differential expression. Silencing might also explain why chromosome inactivation takes place in females so that females do not have twice as many X chromosomes as males. DNA methylation is also used by some genes to differentiate which gene copy is inherited from either the father or the mother, a phenomenon termed imprinting. Cells contain three systems that can interact with each other to silence genes epigenetically. These consist of DNA methylation, histone modifications and RNA-associated silencers.<sup>42</sup>

Many epigenetic changes occur during stress. These changes can be short-lived or last for a lifetime. As an example, many genes

regulating the HPA axis are epigenetically altered by stress. These include genes for CRH, arginine vasopressin and the glucocorticoid receptor.<sup>43</sup> Many epigenetic changes are adaptive and promote changes in the expression of CNS genes that facilitate effective coping with stress.

#### 4. Mechanisms to insure the continuity of the stress response

Numerous mechanisms operate to prevent distraction from the efficacy and continuity of the stress response. The reduction in the capacity to be distracted by pleasurable stimuli is an inherent part of the stress response. During stress, there will be little propensity to sleep, rest, eat or participate in sexual activity. Mood is held fairly constant during stress. This largely reflects some loss of function of the dorsolateral prefrontal cortex, which has a large general role in mediating the capacity to change set.<sup>4</sup>

### MELANCHOLIC VERSUS ATYPICAL DEPRESSION

Before presenting the dysregulation of the stress response in depressive illness, I will address the two subtypes of major depression, melancholic and atypical depression. The extent to which these clinical subtypes represent distinct dysregulations of the stress response will be illustrated in the section on depressive illness.

Melancholic depression belies the term depression in that it is often a state of pathological hyperarousal and anxiety, most notably, about the self. This anxiety, in part, takes the form of feelings of worthlessness, often an important component of the anguish of melancholic depression. Anhedonia is also a key characteristic of melancholia. Melancholic depression prevents the taking of pleasure in what one has achieved or become, pleasures in current everyday life, and hopes for a satisfactory life in the future.

Cognitive changes that occur during stress are exaggerated in melancholic depression. Working memory is compromised, and the shift towards retrieval of reflexive, almost automatic memories is more pronounced. Most likely it is the subgroup of patients with melancholic depression who have multiple physiologic, neuroendocrine and autonomic abnormalities that include hypercortisolism, activation of the central noradrenergic system and increased sympathetic nervous system activity<sup>44</sup> (please see below). Melancholic depression is also associated with insomnia (most often early morning awakening), loss of appetite and loss of interest in sexual activity. Another consistent feature is a diurnal variation in the severity of depressed mood, which is at its worst in the morning, ameliorating modestly as the day progresses. The morning is the time of the maximal activation of the CRH and sympathetic nervous arousal systems,<sup>44</sup> whose activities fall progressively until they reach a nadir in the early morning.

#### Atypical depression

Although both atypical and melancholic depressions are associated with dysphoria and anhedonia, we and others have suggested that melancholic and atypical depression are the antithesis of one another.<sup>45–47</sup> Neurovegetative symptoms in atypical depression consist of lethargy, fatigue, excessive sleepiness, increased food intake, weight gain and depressive symptoms that are lowest in the morning and worsen as the day progresses. As the day progresses, the CRH and noradrenergic systems fall progressively to nadirs that occur in the early morning.

We have shown that patients with forms of atypical depression have evidence of decreased CRH function in the CNS.<sup>46</sup> CRH is an arousal-producing neurohormone whose central administration to rats leads to biological and behavioral responses similar to those seen in melancholia.<sup>19,21</sup> In addition to their CRH status, patients with atypical depression have evidence of lower plasma cortisol

levels than melancholics,<sup>48</sup> though their overall plasma cortisol levels are in the normal range.<sup>48</sup> It should be noted that methodologies other than measurement of basal cortisol levels might be needed to unmask evidence of hypocortisolism. Thus, low cortisol levels could contribute to a disinhibition of the immune system<sup>49</sup> (see below), which may contribute to the proinflammatory state reported in atypical depression.<sup>48</sup>

Atypical depression is also often associated with a disturbing sense of disconnectedness and emptiness. In contrast to melancholics, who seem, at times, bombarded with negatively charged emotional memories, patients with atypical depression often seem walled off from themselves and others. In addition, they may complain of a cognitive and mental fatigue and avoid others, often with the sense that contact would be too demanding, tiring and poorly received. Compared with melancholic depression, atypical depression has an earlier onset and is more frequently chronic. Patients with atypical depression have a significantly higher incidence of childhood and adolescent trauma than those with melancholia.<sup>50</sup>

Rene Spitz made seminal observations regarding developmental abnormalities that befell infants placed soon after birth in understaffed orphanages, where they had little or no sustained human contact. Initially, most of the infants cried bitterly for hours until attended. Subsequently, they withdrew and ceased crying altogether, even if they were left alone or had gone without eating for many hours. In addition, they lost apparent interest in the environment around them.<sup>51</sup> It was as if the trauma of their early deprivation had led to a virtual shutdown of their stress response and affective existence to protect them from enormous distress. Subsequent studies in nonhuman primates who were removed from their mothers and raised by peers reveal a similar behavioral withdrawal in association with hypoactivity of the HPA axis.<sup>52</sup> These may represent very severe forms of atypical depression.

### THE DYSREGULATION OF THE STRESS RESPONSE IN DEPRESSIVE ILLNESS

#### 1. Behavioral responses in depression

*A. Anxiety in depressive illness.* In a seminal study by Drevets *et al.*,<sup>13</sup> patients with depressive illness were shown to have as much as a 40% decrement in the volume of the subgenual prefrontal cortex,<sup>53</sup> in part, attributable to a loss of glial cells that have a key role in removing glutamate from the synapse. Neurons had decreased arborizations and spine densities, and were atrophied but not lost. This loss of neuroplasticity also contributed to the loss of volume, which often correlated with the length and severity of the depression.

The metabolic activity of the subgenual prefrontal cortex was increased,<sup>53</sup> accompanied by a decrease in its capacity to restrain the amygdala and perform other functions associated with the nonstressed state.

In contrast to the decreased volume of the subgenual prefrontal cortex in depression, the amygdala is often enlarged and shows increased dendritic arborizations and spine densities. The metabolic activity of the amygdala is increased during depression, leading to increased anxiety.<sup>13,15</sup> As noted, a vicious cycle can occur between a disinhibited amygdala and a suppressed subgenual prefrontal cortex. The vicious cycle in the positive reverberatory loop between the subgenual prefrontal cortex and the amygdala is much less well-regulated in depression than during normal stress. This loss of regulation is likely to reflect many abnormalities in stress system regulation, including those in BDNF activity, neuroplasticity and neurogenesis (please see below). Substantial hypercortisolism, a markedly hypernoradrenergic state (please see Figure 1) and a disinhibited glutamate system also contribute.



The anterior hippocampus is hypermetabolic in depression. This occurs early in the course of depression. This hypermetabolic state may be linked to the hypermetabolism (the stressed state) of the amygdala and the hypermetabolism (stressed state) of the subgenual prefrontal cortex via monosynaptic connections.<sup>14</sup>

Chronic or inescapable stress in rats causes a similar loss of neuroplasticity in the analog of the subgenual prefrontal cortex and in the hippocampus.<sup>9</sup> There is also loss of synaptic associated proteins such as synapsin 1 and postsynaptic density protein.<sup>9</sup>

The clinical importance of the subgenual prefrontal cortex in depression is underscored by a study showing that deep brain stimulation of the subgenual prefrontal cortex ameliorates depressive symptoms in treatment-resistant depression.<sup>54</sup>

Many mechanisms could contribute to the loss of tissue in the subgenual prefrontal cortex including glutamate toxicity, hypercortisolemia, an activated amygdala, a hypernoradrenergic state and a deficiency of central serotonin neurotransmission.<sup>25</sup>

*B. Maladaptive alterations in attention and memory function that promote depression.* In depressed patients, attention is biased towards sad stimuli, and depressed patients have an inability to disengage from them. Patients with depression have an abnormality in the processing of negative stimuli, showing amygdala activation that is more intense and much longer lasting than healthy controls. Increased internalizing of negative emotional stimuli, by letting negative life events influence self-esteem and self-image, facilitate depressive symptoms as well. Rumination, especially about perceived flaws, intensifies the depressed mood. Moreover, a cognitive style characterized by increased pessimism also reinforces the depressed state.<sup>55</sup>

Disner, *et al.*<sup>55</sup> have proposed an anatomic model for the biased attention for negative stimuli in depressed patients that includes the anterior cingulate cortex, dorsolateral prefrontal cortex and the superior parietal cortex. Many other sites are involved as well. The ventrolateral prefrontal cortex is engaged in selecting gaze targets, whereas the dorsolateral prefrontal cortex and the anterior cingulate cortex inhibit the ventrolateral prefrontal cortex to promote a decreased capacity for engagement. The superior parietal sulcus is involved in coordinating shifts in gaze. All the four regions show decreased activity in individuals with depressive illness, compared with controls. Thus, the observed differences in cortical activity between controls and patients reveal that patients with depressive illness are least efficient at selecting stimuli.<sup>55</sup>

When depressed individuals process negative stimuli, they show amygdala activation that is more intense and much longer lasting than healthy controls. Moreover, biased stimulus processing is automatic and exists even if the emotional salience of the stimulus is masked to the conscious mind. In addition, excessive amygdala reactivity persists even after the aversive stimulus is no longer present.<sup>55</sup>

Increased attention to negative stimuli and increased access to negatively charged emotional memories is accompanied by a blunting of responses of the nucleus accumbens in patients with depressive illness. Thus, decreased prefrontal cortex function reduces reward sensitivity of the nucleus accumbens, which, in turn, contributes to the inability of individuals with depressive illness to adaptively alter reward-seeking behavior.

Depressed patients have persistent ruminative thoughts, especially those that remind them of their perceived flaws.<sup>55</sup>

Rumination is associated with activity in regions involved in emotional recall such as the amygdala and hippocampus. In addition, rumination seems facilitated by a broader network that is associated with self-referential thinking. This involves the medial prefrontal cortex, especially the subgenual prefrontal cortex, which is considered to be an important site of internal representation of self, and is associated with both self-referential appraisal and attribution.

Patients with depression have decreased working memory, and the capacity for sequence-based associative cognition, partially reflecting reduction in dorsolateral prefrontal cortex functioning. Rather, they transition to better well-rehearsed, automatic cognitive programs retrieved from basal ganglia and other sites.<sup>4</sup> These changes are much greater than those seen during a normal stress response.

Taken together, biased memory for negative stimuli in depression may be associated with hyperactivity of the amygdala, triggering bottom-up regulation of the hippocampus, caudate and putamen, which may account for depressive recall with recruitment of top-down prefrontal regions.

It has been suggested that the serotonin transporter is a key moderator of pessimism. Elevated synaptic levels of the serotonin transporter facilitate serotonin reuptake, which decreases the availability of synaptic serotonin. This decrement is thought to lead to an increased diathesis for depression. For patients with depression who show marked pessimism, serotonin transporter binding was elevated in the prefrontal cortex, anterior cingulate cortex, putamen and thalamus compared with those who do not manifest pessimism.<sup>55</sup>

Overall, depressed patients interpret even neutral emotional material in a negative fashion and remember it much better than the individuals who are not depressed.<sup>55</sup> This reflects a loss of subgenual prefrontal cortex function and an activated amygdala. When they focus on negative, emotionally charged material, they cannot let go of this focus. This reflects the reduced activity of the dorsolateral prefrontal cortex, which is essential for appropriately shifting set. In addition, depressed patients cannot 'forget' or extinguish negatively charged emotional memories, have preferential access to them and have great difficulty in accessing positive ones. Thus, patients with melancholic depression have much greater access to negatively charged emotional memory than controls, accentuated by a hypernoradrenergic state<sup>44</sup> and substantial hypercortisolism<sup>45</sup> (please see below).

A vicious cycle exists between the propensity to attend to sad stimuli and depression. The preferential attention to sad stimuli heightens depression, and depression heightens the attentiveness to sad stimuli.

*C. Dysphoria and depression.* As noted, the subgenual prefrontal cortex has a prominent role in the experience of dysphoria.<sup>13</sup> Its function in depression is much more impaired than during stress, with greater dysphoria as a result. Moreover, the dorsolateral prefrontal cortex exerts less cognitive control over dysphoria, further heightening the dysphoric state in depression. In addition, dysphoria is promoted in the context of the suppression of nucleus accumbens activity and the resultant anhedonia (please see below). The attentional and cognitive alterations in depression also reinforce dysphoria, which in turn, stimulates further focus on sad stimuli. The magnitude of the hypercortisolism in depression suppresses the nucleus accumbens, in contrast to the mild elevations in levels during stress, which heighten nucleus accumbens activity.

*D. Altered pleasure and reward processing in depression.* Anatomically, the nucleus accumbens is at the center of the interactions between dopaminergic, serotonergic and glutamatergic systems. Functionally, the nucleus accumbens is involved in both normal and abnormal reward processes, in anhedonia, and in loss of motivation. Increases in nucleus accumbens neuronal activity and dopamine release are seen during the experience of rewards.<sup>56</sup> In patients with depression, the activity of the nucleus accumbens is diminished, and there is a negative correlation between anhedonic symptoms and nucleus accumbens responses



to reward. There is also a negative correlation between anhedonia and the volume of the nucleus accumbens.<sup>56</sup>

As noted, the downregulation of the subgenual prefrontal cortex also contributes to anhedonia. The nonstressed subgenual prefrontal cortex exchanges connections with the VTA and ordinarily increases dopamine release in the nucleus accumbens.

The importance of the nucleus accumbens in depression is highlighted by the fact that deep brain stimulation of the nucleus accumbens also ameliorates depressive symptoms in patients with depressive illness. The time course of recovery is generally 6 months or more of treatment.<sup>57</sup>

As depression increases, anhedonia increases. As anhedonia increases, so does depression. This is yet another example of vicious cycles that promote and perpetuate depression.

## 2. Metabolic, hormonal and neurotransmitter activity during depression

**A. Maladaptive activation of the CRH/HPA axis that promote depression.** The CRH system consists predominantly of hypothalamic and amygdala modules. Both components of the CRH system are activated in melancholia and seem diminished in atypical depression. Hypothalamic CRH hypersecretion leads not only to hypercortisolism in depression,<sup>45</sup> but also to activation of the sympathomedullary system.<sup>44</sup> In addition, activation of the hypothalamic CRH module activates the locus ceruleus<sup>20</sup> and inhibits the gonadal, thyroid and growth hormone axes.<sup>1–3</sup> The amygdala CRH system is involved in promoting anxiety, conditioned fear responses and also activates the hypothalamic and locus ceruleus components of the system. Thus, overall activation of CRH activity could contribute to multiple phenotypic components of melancholic depression. As noted, Figure 1 shows the multiple positive feedback loops in which the CRH system is involved in depression. This includes a positive feedback loop in which not only does CRH activate the secretion of norepinephrine, but in which norepinephrine also activates the release of CRH. CRH hypersecretion and hypercortisolism in depression have many adverse effects, as seen in Table 1.

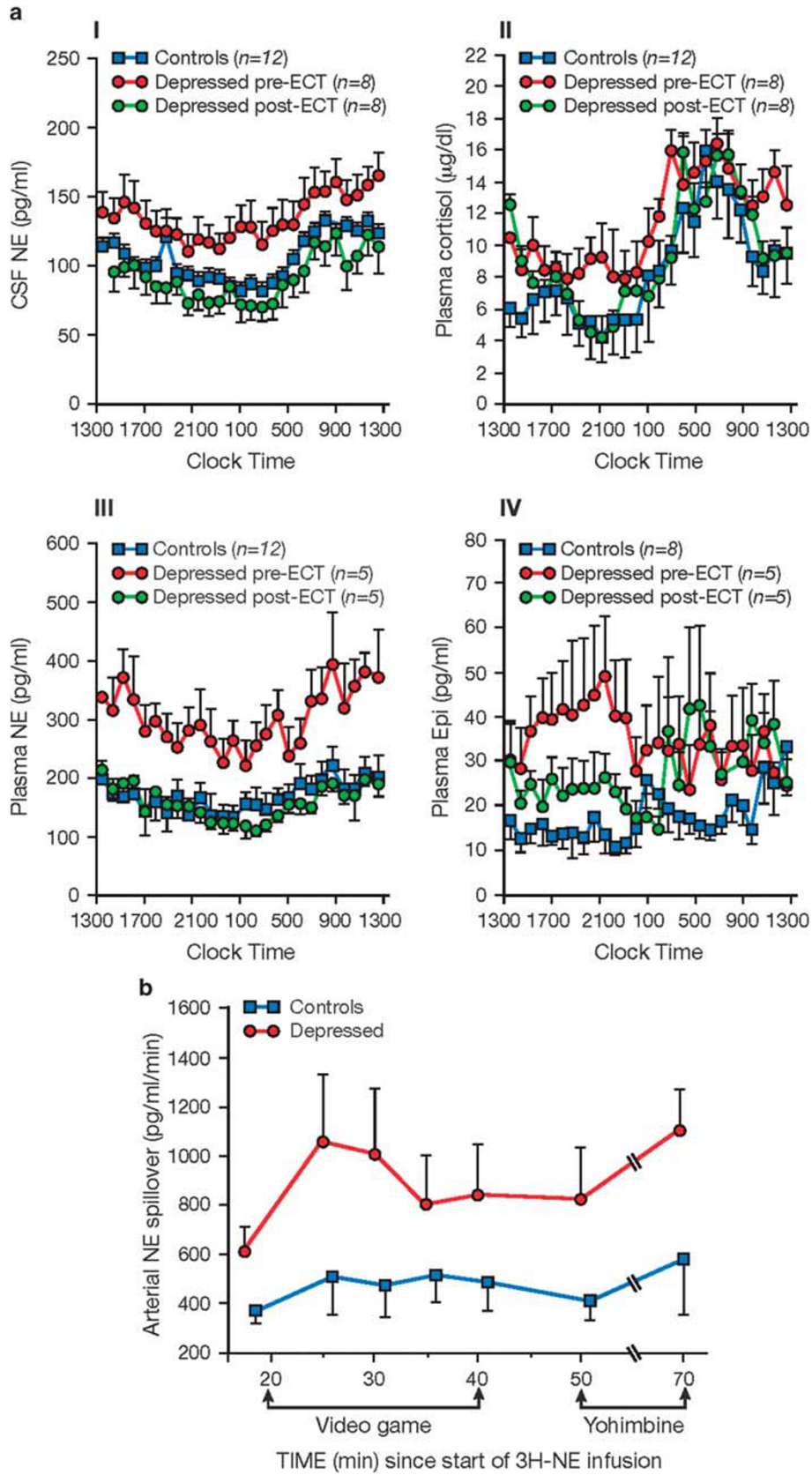
**B. Excessive activation of the locus ceruleus and the sympathetic nervous system that contributes to depression.** The locus ceruleus–norepinephrine system, the sympathetic nervous system, and the adrenal medulla are activated in patients with severe melancholic depression.<sup>44</sup> We found that patients with melancholic depression have significant increases in around-the-clock levels of CSF and

**Table 1.** Adverse effects of the hypersecretion of CRH and cortisol

<b>A. Adverse CNS and peripheral effects of CRH hypersecretion of relevance to melancholia</b>
Anxiety and potentiation of conditioned fear
Neurotoxicity
Inhibition of gonadal, thyroid and growth hormone axes
Activation of the locus ceruleus–norepinephrine system
Inhibition of food intake, sleep and sexual behavior
<b>B. Adverse peripheral effects of CRH hypersecretion of relevance to melancholia</b>
Hypercortisolism
Activation of the sympathetic nervous system
Activation of the adrenomedullary system
Local activation of the innate immune system at sympathetic terminals
<b>C. Adverse CNS effects of hypercortisolism expression</b>
Inhibition of BDNF expression
Inhibition of subgenual prefrontal cortex function
Activation of the amygdala
Potentiation of CRH-mediated locus ceruleus activation
Loss of hippocampal volume, neurogenesis and neuroplasticity
Loss of neuroplasticity in prefrontal cortex
Toxicity to glial cells
Neuronal apoptosis
Interference with cognition
Inhibition of gonadal, thyroid and growth hormone axes at hypothalamic level
Behavioral hyperarousal and insomnia
Disturbances in biological rhythms
<b>D. Adverse peripheral effects of hypercortisolism</b>
Potentiates adrenergic receptor activity
Insulin resistance and its sequella
Activation of the renin–angiotensin system
Activation of endothelin secretion
Inhibition of vasodilatory effects of nitric oxide—endothelial dysfunction
Inhibition of thrombolysis
Hypertension
Loss of bone mass
Increased visceral fat deposition and its proinflammatory sequella
Direct inhibition of thyroid, gonadal and growth hormone secretion in the periphery

Abbreviations: BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CRH, corticotropin-releasing hormone.

**Figure 3.** The hypernoradrenergic state of melancholic depression. **(a)** Hourly around-the-clock sampling of CSF NE, plasma NE, plasma cortisol and plasma epinephrine in severely depressed, medication-free patients with melancholic depression. Patients were studied during depression and after ECT-induced remission. Severely depressed patients had concomitant elevations of the hourly 24-h levels of CSF NE, plasma NE, plasma cortisol and plasma epinephrine. These levels all fell to normal levels after ECT. The diurnal variations of CSF NE, plasma NE and plasma cortisol were virtually superimposable and highly correlated with one another. Their arithmetic means also were highly correlated. These arousal-producing compound levels all peaked at 0800 to 0900 hours, a time when melancholic symptoms are at their worst. Their peaks also coincide with the time for maximal susceptibility to myocardial infarction and sudden death. CSF NE and plasma norepinephrine closely correlate with one another, yet they derive from different sets of neurons. Patients with the Shy Drager syndrome have very low plasma norepinephrine levels in association with robust CSF norepinephrine concentrations. Excessive central norepinephrine secretion in melancholia exerts several adverse effects. Norepinephrine inhibits critical structures in the prefrontal cortex such as the subgenual and dorsolateral prefrontal cortices. NE stimulates the amygdala and the CRH/HPA axis. Central noradrenergic excess also contributes to hypertension, activation of the HPA axis and the sympathetic nervous system. **(b)** Norepinephrine spillover in mild–moderately depressed unmedicated patients with melancholic depression. Patients were given an IV dose of tritiated NE to control for clearance rate, allowing calculation of spillover. Depressed patients had significantly higher baseline NE spillover, and significantly higher levels after a mildly stressful video game and after yohimbine, an alpha-2 antagonist that increases the release of norepinephrine. Peripheral hypersecretion of norepinephrine leads to hypertension and its sequella, increased blood viscosity, sodium retention, increased IL-6 secretion, insulin resistance, increased cardiac oxygen consumption, significant increases in the adverse outcomes of congestive heart failure, including death. CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; ECT, electroconvulsive therapy; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; NE, norepinephrine.



plasma norepinephrine, plasma cortisol and plasma epinephrine levels measured hourly for 24 consecutive hours.<sup>44</sup> Melancholic patients also have increased norepinephrine spillover into arterial plasma at rest and in response to stressors<sup>44</sup> (Figure 3). The noradrenergic system is involved in multiple positive feedback loops with other mediators of depression (Figure 1). These data demonstrate the 24-h concordance in the activation of the HPA axis and the locus ceruleus–norepinephrine system. The positive correlation in the 24-h levels of norepinephrine and cortisol is virtually as great as that from plasma adrenocorticotrophic hormone and plasma cortisol.<sup>44</sup>

**C. Monoaminergic neurotransmitters during depression.** A review of monoaminergic neurotransmitters in depression is beyond the scope of this review. As noted, norepinephrine is hypersecreted in melancholic depression.<sup>44</sup> In the CNS, norepinephrine from the locus ceruleus produces arousal, alarm, and increases the signal-to-noise ratio in the various components of the stress system. Excessive norepinephrine release activates the amygdala and takes the medial prefrontal cortex off line. Several lines of evidence implicate reduced dopaminergic activity in depression. Serotonin neurotransmission is also thought to be generally reduced in depression. Ordinarily, serotonin reduces the metabolic activity of the subgenual prefrontal cortex, resulting in this key structures being in the nonstressed state. A decrement in serotonin neurotransmission and a deficient activation of post-synaptic 5HT-1a receptors increases the metabolic activity of the subgenual prefrontal cortex, thus promoting the stressed state. Similarly, 5HT decreases the firing rate of the amygdala. Taken together, a deficiency of serotonin-1A activity promotes two of the cardinal manifestations of depression, the stressed states of both the subgenual prefrontal cortex and the amygdala.<sup>25</sup>

**D. Activity of the glutamate system during depression.** Glutamate is the principal excitatory neurotransmitter in brain and is released at 50% of the synapses in the brain. Excessive glutamate in the synapse classically leads to glutamate neurotoxicity associated with loss of neurogenesis, neuroplasticity, neuronal atrophy, and an effective endoplasmic reticulum stress response. As glutamate is cleared primarily by amino-acid transporters produced by glial cells, the loss of glial cells in the prefrontal cortex and hippocampus in patients with depression, resulting in increased glutamate transmission, is likely to be contributory to the loss of tissue in these locales. This hypothesis is supported by data showing that NMDA receptor antagonists attenuate stress-induced atrophy of CA3-pyramidal neurons. Furthermore, infusion of ketamine, an NMDA antagonist, produces rapid amelioration of stress-induced loss of neuroplasticity in experimental animals (please see below).<sup>8</sup>

Glutamate is released during acute stress, and this elevation is sustained during chronic stress or chronic corticosterone administration.<sup>19</sup> Chronic stress also decreases its clearance by glial transport proteins that remove glutamate from the synapse. During chronic stress, there is also increased release of glutamate, as well as increased glutamate receptor expression, all leading to potentiated glutamate neurotransmission and potential neuronal injury.

Ketamine is an antagonist of the glutamate NMDA receptor. Ketamine has the unique property of rapidly inducing remission of depression in treatment-refractory patients with depressive illness within 2 h of its administration. Effects last as long as 7–10 days.<sup>58</sup> The fast efficacy of ketamine is a remarkable development and opens up the glutamate system as a prime target for rapidly promoting neuroplasticity and neurogenesis and in treating depression.

Ketamine depends on BDNF for its therapeutic efficacy.<sup>59</sup> Overexpression of the Met allele of BDNF results in impaired BDNF function and blocks the synaptogenic effects of ketamine. This finding is compatible with *in vitro* studies demonstrating that

release of BDNF is required to produce synaptic changes. Activity-dependent release of BDNF might also account for the fact that ketamine is more rapid and efficacious than conventional antidepressants, which increase mRNA expression, but not the release of BDNF.

GLYX 13, an NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects in experimental animals. In contrast to ketamine, it activates rather than down-regulates NMDA receptors.<sup>60</sup> In studies involving patients with depressive illness, the NMDA receptor-activating compound sarcosine also induces antidepressant effects.<sup>61</sup> Their mechanisms of action are unknown, but might indicate that substantially perturbing the NMDA receptor in depressed patients is therapeutic.

In positron emission studies, the metabolic activity of the subgenual prefrontal cortex is elevated compared with metabolic activity monitored during the recovered state.<sup>14</sup> The metabolic activity of the subgenual prefrontal cortex is an index of glutamate metabolism. Depressed patients have evidence of increased glutamate activity in association with a decrease in GABA neurotransmission. A recent genome-wide association study revealed a highly robust relationship between glutamine decarboxylase 1 and the therapeutic response to lithium ( $P < 10^{-37}$ ).<sup>62</sup>

**E. Inflammation, insulin resistance and a prothrombotic state in depression.** Many patients with depressive illness have signs of premature aging. Compared with the general population, they have an earlier onset and a significantly higher rate of coronary artery disease,<sup>63</sup> stroke<sup>64</sup> and type 2 diabetes.<sup>65,66</sup> We showed that even premenopausal women with major depression have pathologic loss of bone mass.<sup>67</sup>

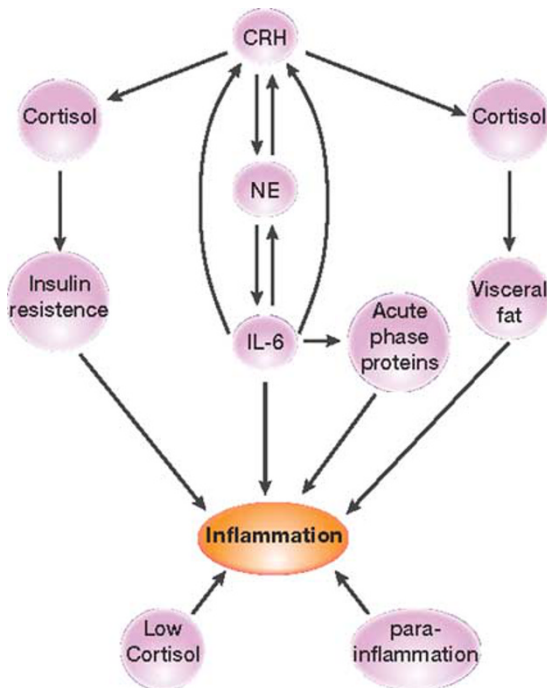
Patients with depressive illness lose an estimated loss of life of 7 years. Supporting these epidemiological data is the finding that patients with depressive illness have telomere loss estimated to reflect 7 years of telomere growth.<sup>68</sup>

The premature aging and death of patients with depressive illness reflects many pathophysiological mechanisms (Figure 4 and text). These include increased secretion of proinflammatory cytokines and acute-phase proteins into plasma,<sup>69</sup> the simultaneous activation of the CRH system and hypercortisolism, increased CNS norepinephrine secretion, increased sympathetic outflow, a prothrombotic state<sup>70</sup>, and increased cytokine release in the brain. As a consequence, depression is associated with inflammation, insulin resistance<sup>71</sup> and a prothrombotic state (please see below).<sup>70</sup>

**Inflammation. Six possible pathways to peripheral inflammation in depressive illness.** Patients with major depression are in a pro-inflammatory state, and many studies indicate that this state is relevant to the central and peripheral manifestations of depressive illness. Studies have shown increases in plasma mediators of the innate immune system such as IL-6, gamma-interferon, TNF- $\alpha$ , C-reactive protein and serum amyloid A (please see Figure 4).

1. Activation of the hypothalamic CRH system leads to the release of norepinephrine into the systemic circulation. Norepinephrine stimulates IL-6 production,<sup>28</sup> and both norepinephrine<sup>31</sup> and IL-6 stimulates the acute-phase response.<sup>72</sup> The acute-phase response is a stereotyped response that consists of a series of over 20 hepatic proteins. Many acute-phase response proteins, including C-reactive protein and serum amyloid A, have clear proinflammatory effects. We found that medication-free remitted patients with major depression had significant increases in C-reactive protein and serum amyloid A studied on two separate occasions<sup>72</sup> (Figure 4).
2. A second cause of the proinflammatory state of depression occurs because of an indirect effect of CRH-mediated hypercor-





**Figure 4.** Mechanisms for medical consequences of melancholic depression. CRH stimulates the sympathetic nervous system with release of NE into the systemic circulation. Norepinephrine goes on to mediate a number of other responses. Norepinephrine stimulates CRH, IL-6 and the acute-phase stress response. The acute-phase response consists of over 20 proteins, which modulate inflammation and lead to a mild prothrombotic state. CRP and fibrinogen are acute-phase reactants and are elevated in depression. Cortisol and norepinephrine lead to insulin resistance and mild hyperinsulinism. Insulin stimulates the sympathetic nervous system and is proinflammatory. Cortisol promotes the enlargement of the visceral fat mass, which contains a host of proinflammatory cytokines such as IL-6 and TNF- $\alpha$ . IL-6 correlates positively with BMI so that BMI matching is important in clinical studies to control for the impact of cytokines. Increased visceral fat has a large role in obese patients in contributing to the metabolic syndrome. Patients with depression can have an increased visceral fat mass with a perfectly normal BMI because of the impact of cortisol on visceral fat. The collective impact of neuroendocrine, proinflammatory and prothrombotic processes that occur during a normal stress response can, when exaggerated in depression, result in premature coronary disease, stroke, type 2 diabetes and osteoporosis. These are preventable and clinicians should check carefully for these stigmata in their depressed patients. There are multiple positive feedback loops in this circuit that amplify its overall intensity. There are also multiple stimuli to specific physiologic responses. For instance, IL-6, the acute-phase response, hyperinsulinism, increased visceral fat mass and low plasma cortisol levels, all promote an inflammatory response. BMI, body mass index; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; IL, interleukin; NE, norepinephrine; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

tisolism. Although cortisol has a number of anti-inflammatory effects, many proinflammatory genes respond to cortisol. Of greater importance is the effect of glucocorticoids to induce a highly significant increase in the deposition of visceral fat in the omentum<sup>73</sup> (Figure 4). We now know that visceral fat is a highly active endocrine and proinflammatory tissue. As the visceral fat mass expands, many macrophages invade it and release inflammatory cytokines such as TNF-1,  $\gamma$ -interferon, IL-6 and others into the systemic circulation.<sup>29</sup> It is estimated that 40% of circulating IL-6 emanates from visceral fat. There is a positive correlation between the visceral fat mass and levels of plasma

IL-6.<sup>74</sup> Even mildly obese children are in a proinflammatory state.<sup>75</sup> In addition, visceral fat releases many compounds that influence CNS function and the CNS significantly influences the size and composition of visceral fat.

Most people with increased visceral fat are overweight or obese. Normal weight patients with depressive illness have an increase in visceral fat mass secondary to hypercortisolism that is similar to the visceral fat mass observed in obese patients. This state of 'pseudo-obesity' in depression significantly contributes to the proinflammatory state of depression as well as other metabolic stigmata of depression (see below). We have found that patients with melancholic depression have a significant loss of lean body mass and a significant increase in total adiposity. Thus, patients with depressive illness may have features of the metabolic syndrome even though they are at normal weight (Gold *et al.* unpublished observations).

- As noted, many patients with depressive illness are insulin resistant and have hyperinsulinemia.<sup>71</sup> Insulin is a highly proinflammatory compound.<sup>29,32</sup>
- In addition to CRH, insulin also activates the sympathetic nervous system further promoting inflammation.<sup>76,77</sup> Some have speculated that the impact of hyperinsulinism on inflammation and the sympathetic nervous system is to set into motion a counter-regulatory apparatus for limiting unwanted excessive weight gain during periods of overfeeding.<sup>32</sup>
- A fifth possible mechanism for the inflammation of depressive disorders is the presence of parainflammation, proposed by Medzhitov<sup>78</sup> at Yale. Parainflammation occurs in response to stressors such as overfeeding and aging that were not present during our early evolutionary history, and for which we are not adequately prepared. These also include insufficient exercise, modern lighting, novel foodstuffs and drugs.<sup>76</sup> We extend that concept and hypothesize here that the frequent, if not daily, occurrence of acute social stressors that go on for extended periods also represents a stimulus to which early humans were not exposed. Hence, I postulate that major depression is associated with a parainflammatory state (please see Figure 4). The difference between classical inflammation and parainflammation is that the latter does not occur in response to pathogens or tissue damage, but rather from alterations in the homeostatic set-point in specific tissues in response to stressors such as those involving nutrient-sensing energy.<sup>78</sup> The most prominent markers for parainflammation are smoldering low level increases in the concentrations of acute-phase proteins, C-reactive protein and serum amyloid A. These are seen in another parainflammatory illness, coronary artery disease that, like some forms of depression, is a disease attributable, in part, to overeating, under exercising and psychological stress.
- Hypoactivity of the hypothalamic CRH neuron, as seen in some patients with atypical depression<sup>46,47</sup> is a sixth potential cause of inflammation in depressive illness (Figure 4). Cytokines are very potent stimuli to the hypothalamic CRH neuron and plasma cortisol secretion.<sup>27</sup> We have shown in an experimental model of inflammation that a congenital hypoactivity of the hypothalamic CRH neuron in response to inflammatory mediators, with a resultant decreased rise in plasma cortisol levels, results in a proinflammatory state. Thus, a clinically relevant negative feedback response occurs in which cytokine mediated cortisol release restrains the immune response from overshooting.<sup>49</sup> Low levels of cortisol lead to a disinhibition of the immune system. Patients with hypocortisolism due to Addison's disease are in a proinflammatory state for this reason.

Special roles of peripheral and central cytokines in the pathophysiology of depressive illness: The release of cytokines during the peripheral stress response is particularly important, and beyond their roles in inflammation, they are extremely potent stimuli to

many components of the peripheral stress response. Specifically, at extremely low concentrations, cytokines activate the CRH system and the HPA axis,<sup>27</sup> the sympathetic nervous system,<sup>28</sup> promote insulin resistance<sup>32</sup> and activate multiple components of the coagulation system.<sup>30</sup> They also stimulate the acute-phase response.<sup>31</sup>

Systemic administration of cytokines produces a depressed state.<sup>79</sup> Thus, cytokines in the periphery can gain access to the CNS via facilitated transport or through fenestrations in the blood brain barrier.<sup>80</sup> IFN- $\alpha$  given to humans decreases CSF 5HIAA and increases the levels of CSF IL-6.<sup>81</sup> Peripheral activation of the innate immune system, leading to increased proinflammatory cytokine production, decreases neurotrophic support and neurogenesis in hippocampus.<sup>81</sup>

Cytokines are also produced locally in the CNS.<sup>33</sup> Cytokines influence the synthesis, release, reuptake and metabolism of monoamines,<sup>33</sup> increase glutamate release<sup>82</sup> and decrease the expression of glutamate transporters on relevant glial elements, hence decreasing glutamate uptake.<sup>81</sup> They contribute to the decrease in neuroplasticity and neurogenesis, promote oxidative stress and induce apoptosis in glial cells. Thus, they are likely to have a key role in the loss of glia in the subgenual prefrontal cortex, the dorsolateral prefrontal cortex and the hippocampus, and contribute to the loss of tissue and function in these loci. In addition, chronic stress-induced changes on behavior, cognition, neurotrophic factors and neurogenesis can be prevented by blockade of CNS cytokine activity via administration of the IL-1 receptor antagonist or by neural precursors or cells overexpressing the IL-1 receptor antagonist.<sup>83,84</sup> CNS cytokines also have many neuroendocrine effects. They activate the central CRH system and the HPA axis,<sup>27</sup> contribute to glucocorticoid receptor down-regulation,<sup>85</sup> and inhibit the growth hormone and gonadal axes.<sup>3</sup> As part of their capacity to promote a depression-like phenotype, they also interfere with cognitive function.<sup>85</sup> Insulin resistance and a prothrombotic state in depressive illness: Insulin resistance occurs in depression for multiple reasons.<sup>71</sup> Hypercortisolism is a potent stimulus to insulin resistance.<sup>32,85</sup> Insulin promotes inflammation.<sup>32</sup> Inflammation, in turn, is a potent stimulus to insulin resistance.<sup>32</sup> Rarely does one occur without the other. Thus, insulin and inflammation are involved in a positive feedback loop.<sup>32</sup>

A prothrombotic state is also characteristic of depressive illness.<sup>70</sup> Acute-phase proteins include four highly prothrombotic mediators, factor VIII, prothrombin, plasminogen activator inhibitor-1 (a potent suppressor of thrombolysis) and von Willebrand factor. We have shown that factor VIII and plasminogen activator inhibitor-1 levels are elevated in young women with major depression.<sup>70</sup>

Taken together, inflammation, hypercortisolism, insulin resistance, an activated central and peripheral noradrenergic system, an activated central and peripheral system of cytokines and a prothrombotic state, work together to induce the medical consequences of depression (Figure 4 for mechanisms).

Multiple positive feedback loops exist within the system involved in the proinflammatory state of depression (please see Figure 4), and between inflammatory mediators and other components of the stress response such as the CRH/HPA axis and the noradrenergic system, and their feedback loops.

3. Failure to effectively provide neuronal protection during the extra demands of stress contributes to depression

**A. Depression and brain-derived neurotrophic factor.** A role for BDNF in depression was first postulated in a seminal paper by Duman, *et al.*<sup>86</sup> Uncontrollable and prolonged stress or sustained hypercortisolism in experimental animals results in a depressive phenotype and a decrease in the expression of BDNF in the prefrontal cortex and hippocampus. The decrease in BDNF contributes to structural changes, including abnormal dendritic and synaptic

architecture in prefrontal cortex and hippocampus.<sup>8,34</sup> Uncontrollable and prolonged stress also reduces neurogenesis in the hippocampus, associated with depletion of BDNF.<sup>8,34</sup> These changes are hypothesized to contribute to the reduced volume of the prefrontal cortex and hippocampus in depressed patients. These deleterious effects of stress on BDNF depletion can be blocked by the administration of antidepressants.<sup>8</sup>

Other studies in experimental animals confirm the salutary effects of BDNF on neurogenesis and neuroplasticity. Studies utilizing RNA interference to knock down BDNF expression in the hippocampus results in depressive behaviors.<sup>34</sup> Mutant mice with a heterozygote knockout of the BDNF gene, which leads to the expression of half the usual levels of BDNF, display normal behavior at baseline, but exhibit a depressive phenotype when moderately stressed.<sup>34</sup> Overexpression of the BDNF Met polymorphism in mice decreases the number and length of apical dendrites in hippocampal CA3 neurons.<sup>34</sup>

Patients with depressive illness have decreased plasma levels of BDNF.<sup>87</sup> Depressed patients with the BDNF Met polymorphism, which decreases the activity of BDNF, have smaller hippocampi than depressed patients with the normal variant.<sup>34</sup> This decrement in neuroplasticity is similar to that seen after chronic or inescapable stress. BDNF is also essential for the therapeutic effects of ketamine<sup>38</sup> (please see below).

Cortisol and BDNF participate in a potential vicious cycle. Cortisol inhibits BDNF and cortisol levels go up when BDNF activity is reduced.

**B. Loss of neuroplasticity in depression.** Postmortem brains taken from depressed patients reveal reductions of dendritic arborizations and spine density in neurons of the subgenual prefrontal cortex and the hippocampus.<sup>9</sup> These deficits were also demonstrated in the dorsolateral prefrontal cortex. The neuroplastic abnormalities in the subgenual prefrontal cortex resolve in the context of long-term, but not acute, administration of antidepressants.

In contrast to the subgenual prefrontal cortex and the hippocampus, the size of the amygdala is increased during depression. Postmortem brains taken from depressed patients reveal significant increases of dendritic arborizations and spine density in neurons in the amygdala.

**C. Neurogenesis in depression.** Inhibition of neurogenesis delays the return to baseline of glucocorticoid release in response to stress.<sup>41</sup> Thus, neurogenesis is essential to a normal stress response. In chronically stressed rats leading to depression-like features, neurogenesis is significantly suppressed. Antidepressants, however, restored neurogenesis with a lag time similar to the delay that patients experience in responding to antidepressants. This reflects the time of neuronal maturation in adult hippocampus.<sup>88</sup> If neurogenesis is prevented, the antidepressant response does not occur.<sup>89</sup>

Neurogenesis and HPA activity have reciprocal interactions. HPA axis-mediated cortisol secretion suppresses neurogenesis. Neurogenesis, in turn, reduces the duration and the magnitude of the cortisol response to stress.<sup>41</sup>

Prolonged uncontrollable stress depletes BDNF to decrease cognitive functions dependent on the capacity for pattern separation. This deficit in pattern recognition exacerbates the ability to cope with incoming stressful stimuli.<sup>40</sup> Thus, a vicious cycle can occur with chronic uncontrollable stress decreasing pattern recognition, which further compromises the capacity to deal with further stressors.

Unraveling the mechanisms by which chronic uncontrollable stress diminishes neurogenesis should provide important new targets for the design of new antidepressants.

**D. Relevance of the endoplasmic reticulum stress response to depression.** Patients with bipolar disorder have been reported

to have a polymorphism in the XBP-1 gene, associated with decreased expression of XBP-1 (Figure 2).<sup>11</sup> Normally, XBP-1 is crucial to the activation of the endoplasmic reticulum-associated degradation (ERAD) program and increases in chaperones such as GRP 78. BDNF is a potent stimulus to XBP-1.<sup>10,11</sup>

Valproate exerts multiple effects to influence the ER response in favor of cell rescue. These effects occur, in part, via stimulation of the ATF6 branch of the ER stress response. ATF6 is the gene upstream of XBP-1 and is a potent stimulus to XBP-1 expression. Valproate also exerts a stimulatory effect on the production of chaperones and on the ERAD response independent of its effect on ATF6 (Figure 2).<sup>11</sup>

Lithium also exerts multiple effects on the endoplasmic reticulum stress response in favor of cell rescue.<sup>11</sup> Lithium promotes the expression of chaperones and Bcl-2. Both valproate and lithium inactivate glycogen synthase kinase 3 (GSK-3), which transduces many downstream effects that occur in the context of activation of the endoplasmic reticulum stress response, leading to apoptosis. Mutation of the WFS1 protein leads to Wolfram's Syndrome, which is associated with endoplasmic reticulum stress and a high incidence of serious affective illness.<sup>11</sup>

Many aspects of the pathophysiology and treatment-response of depressed patients suggest involvement of a deficient endoplasmic reticulum stress response. (Figure 2).<sup>11</sup> Therapeutic strategies at enhancing the activity of the endoplasmic reticulum stress response could potentially have antidepressant effects. Agents to enhance the production of chaperones are among those that might be effective.

*E. Epigenetic changes in depression.* We now know that epigenetic changes influencing gene expression in stress-responsive genes in limbic regions contribute to the pathophysiology of depressive illness and other stress-related illnesses such as posttraumatic stress disorder.<sup>42,43,90</sup> These changes can be for short periods or can last for a lifetime. With respect to depressive illness, epigenetic changes can influence the impact of stress on the precipitation of a depressive episode, the effects of antidepressant treatment and the effects of early stress on subsequent stress vulnerability.<sup>43</sup> Possible transmission of stress-induced epigenetic abnormalities from parent to offspring is supported by circumstantial evidence but not proven definitively.<sup>91</sup>

There is strong inter-individual variability to stress so that many people are resilient, enduring tremendous stress without behavioral or biological consequences. Others are very sensitive to stress and exhibit many epigenetic changes. Thus, susceptibility to depression represents genetic vulnerability to the effects of stress on genes expressed in the limbic system or elsewhere in brain, and the range of stressful stimuli accumulated over a lifetime that promote lasting epigenetic changes. Epigenetics have a key role in neuronal plasticity, as evidenced by changes in learning and memory, social and maternal behavior and pathological entities such as depression.<sup>43,91</sup>

Epigenetics will improve our understanding of the regulation of the stress response and its dysregulation in depressive illness. In animal models of stress, several key stress genes have already been identified as being epigenetically altered including the genes for CRH, the glucocorticoid receptor and for arginine vasopressin.<sup>43</sup> Isolating the range of stress-induced changes in epigenetic regulation in multiple genes in multiple brain regions will be labor-intensive, but should yield important information about the regulation of the response to stressors, differentiate vulnerable from resilient individuals, identify factors involved in the pathogenesis of depression and provide targets for new antidepressants.<sup>43</sup> For example, we already know that valproate influences epigenetic processes by interacting with histones via histone deacetylase.<sup>91</sup>

4. Mechanisms that promote the perpetuation of the depressed state

Numerous mechanisms operate to lock depressed patients in the depressed state. As noted, multiple positive reverberating feedback loops get established during the depressed state that are extremely difficult to break. During melancholic depression, the early insomnia is likely to exacerbate the depressed state and interfere with its resolution. Mood is clamped in a depressed, fearful mode, reflecting a loss of dorsolateral prefrontal cortex function that ordinarily promotes adaptive changes in set. Depressed patients are compromised in their capacity to experience pleasure, adaptive during ordinary stress, but maladaptive in depression.

#### SUMMARY

Depression affects ways of feeling and thinking that intrude upon the features that help define our humanity. It is a neurodegenerative disease that affects key sites of the prefrontal cortex, limbic system and multiple cortical areas. In its severe manifestations, it is like a cancer of the self that impairs our self-respect, sense of well-being and capacity to think clearly. It 'metastasizes' from the brain to the periphery to influence the functional integrity of the HPA axis and the SNS system, and is associated with a prothrombotic state, inflammation and insulin resistance. Taken together, these phenomena contribute to multiple systemic pathologies. Ubiquitous systems in brain, such as the glutamate and GABA neurotransmitter systems, are affected and genetic alterations in key regulatory components of these systems have been identified.

During brief, controllable stress, many adaptive mechanisms circumscribe the stress response so that it is activated only when it is needed. They include effective neuroplasticity, neurogenesis, endoplasmic reticulum stress, epigenetic adaptations, maintenance of normal feedback set-points for multiple biological processes and the ability to circumvent potential vicious cycles. Because there are multiple, redundant positive feedback loops operating in the cascade of stress-related biological events, these interact with the burden of aversive emotional memories, life stressors and genetic vulnerability to render the stress system particularly vulnerable to becoming dysregulated and hyperactive in depression. The expected cascading of the stress system in the context of preferential attention to sad stimuli and the escalation of depressive symptoms adds a further burden of vicious cycles. Although fundamentally pathological, one can wonder whether the loss of tissue and function of the subgenual prefrontal cortex represents one of nature's last-ditch efforts to activate the stress response as much as possible. It is possible that the treatment of depression, like the treatment of hypertension, requires multiple interventions at various sites in the stress system cascade to effectively treat depressions, which have not otherwise responded to available interventions.

Given that the stress system is the vulnerable target in depressive illness, it is not surprising that significant stressors early in life or throughout adulthood influence the susceptibility to depression, its severity and its natural history. Depression clearly falls at the intersection of genetic vulnerability with disturbing life experiences encoded in emotional memory. This intersection helps us to understand how psychotherapy can influence a disorder with biological vulnerability that is also responsive to medication.

Some argue that depression confers adaptive advantages during threatening situations by discouraging exploration, sleep and distractions by pleasurable stimuli. I have a different concept of depressive illness. I see depression as a disorder of the stress response, an adaptive response that we ordinarily need for survival. It can be analogized to another group of diseases of adaptation, autoimmune disorders, which are dysregulations of



the immune system. In my estimation, full-blown depression confers no greater adaptive advantage than systemic lupus erythematosus.

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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