

GRAND ROUNDS

Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states

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Stress precipitates depression and alters its natural history. Major depression and the stress response share similar phenomena, mediators and circuitries. Thus, many of the features of major depression potentially reflect dysregulations of the stress response. The stress response itself consists of alterations in levels of anxiety, a loss of cognitive and affective flexibility, activation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system, and inhibition of vegetative processes that are likely to impede survival during a life-threatening situation (eg sleep, sexual activity, and endocrine programs for growth and reproduction). Because depression is a heterogeneous illness, we studied two diagnostic subtypes, melancholic and atypical depression. In melancholia, the stress response seems hyperactive, and patients are anxious, dread the future, lose responsiveness to the environment, have insomnia, lose their appetite, and a diurnal variation with depression at its worst in the morning. They also have an activated CRH system and may have diminished activities of the growth hormone and reproductive axes. Patients with atypical depression present with a syndrome that seems the antithesis of melancholia. They are lethargic, fatigued, hyperphagic, hypersomnic, reactive to the environment, and show diurnal variation of depression that is at its best in the morning. In contrast to melancholia, we have advanced several lines of evidence of a down-regulated hypothalamic-pituitary adrenal axis and CRH deficiency in atypical depression, and our data show us that these are of central origin. Given the diversity of effects exerted by CRH and cortisol, the differences in melancholic and atypical depression suggest that studies of depression should examine each subtype separately. In the present paper, we shall first review the mediators and circuitries of the stress system to lay the groundwork for placing in context physiologic and structural alterations in depression that may occur as part of stress system dysfunction.

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Stress precipitates major depression and influences its incidence, severity and course.^{1,2} The stress response and major depression share many features because of similar brain circuitries and mediators (reviewed in ^{3–5}). Each is associated with a diminution of cognitive and affective flexibility, alterations in arousal, and perturbations in neuroendocrine and autonomic function (reviewed in ⁵). Because major depression is a heterogeneous disorder, we focus here on two subtypes, melancholic and atypical depression. Our data and those of others indicate that the principal arousal producing mediators of the stress response, such as the corticotropin releasing hormone (CRH) system, are hyperactive in melancholic depression.⁶ Not surprisingly, melan-

cholia is associated with anxiety, dread of the future, insomnia, loss of appetite, and hypothalamic-pituitary-adrenal activation.³ Atypical depression seems to be the reverse of melancholia, in that it is characterized by lethargy, fatigue, hypersomnia and hyperphagia.⁵ We have advanced several lines of evidence of a downregulated hypothalamic-pituitary adrenal axis in atypical depression, and our data show us that it is of central origin.^{3,7} In the present paper, we shall first review the mediators and circuitries of the stress system to lay the groundwork for placing in context physiological and structural alterations in depression that may occur as part of stress system dysfunction. We shall then provide an overview of critical stress mediators and structures that we postulate lay significant roles in the pathophysiologies of melancholic and atypical depression.

We would like to emphasize at the outset that the majority of patients with major depression present

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with a mixture of cognitive, affective, and physiologic features that do not fully conform to the classifications of melancholic and atypical depression. Moreover, not all cases of melancholic and atypical depression resemble one another. We also do not suggest here that abnormalities in the stress system are primary factors in the pathophysiology of depression. Rather, we feel that stress mediators, as likely downstream elements in depressive pathophysiology, transduce many of the clinical and physiological alterations we are currently able to decipher. Therefore, further elucidation of stress system dysfunction in patients with major depression could provide improved targets for systematic research, diagnosis, treatment, and prevention.

Major depression

Major depression is a heritable disorder that affects approximately 8% of men and 15% of women.¹ For over 75% of patients, major depression is a recurrent, lifetime illness, characterized by repeated remissions and exacerbations.⁸ Over 50% of patients who recover from a first depressive episode will have a second within 6 months unless they are given maintenance antidepressant treatment.² For those who never receive treatment, as many as 15% will succumb to suicide.⁹

Depression not only causes great mental anguish but also intrudes upon fundamental biological processes that regulate sleep, appetite, metabolic activity, autonomic function, and neuroendocrine regulation (reviewed in ^{4,8}). These disturbances are likely to contribute to premature coronary artery disease,^{10–12} premature osteoporosis,¹³ and the doubling of mortality in patients with major depression at any age independent of suicide, smoking, or significant physical illness.^{10–12} In taking into account the natural history, mental suffering, and medical morbidity associated with major depression, the World Health Organization ranked this disorder as one of the leading causes of disability worldwide.¹⁴

It is now clear that a history of childhood trauma increases the risk for depression in adulthood. Moreover, environmental stress or internal conflict during adult life can precipitate major depression and influence its course and severity.¹⁵ Thus, susceptibility to major depression includes burdens of internal conflict and external stressors, as well as the sum, intensity, and accessibility of emotional memories that recall past abandonment, failure, or abuse.

Classification of depression

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) is the principal instrument for psychiatric diagnoses in the United States.¹⁶ The DSM-IV lists two major divisions of depressive subtypes based on the phenomenology of recurrent affective episodes rather than the clinical phenotype of the depression. Bipolar affective illness is associated with recurrent bouts of both major depression and mania or hypomania, affects 1–2% of the population, and occurs with equal frequency in men and women. Major depression

is characterized by recurrent bouts of major depression alone, occurs in approximately 12% of the population, and presents with a 2:1 female preponderance. Both disorders are heritable and involve multiple genes.^{17,18}

Epidemiological studies suggest overlap in genetic and environmental factors predisposing to bipolar or unipolar disorder. As an example, the offspring of bipolar parents have a higher incidence of both bipolar illness and unipolar illness than the general population. First degree relatives of patients with unipolar illness also have a smaller increase in the incidence of major depression.¹⁹

The DSM-IV lists two distinct clinical depressive syndromes that seem the antithesis of one another, melancholic and atypical depression. This distinction is based on the pattern of psychological and neurovegetative symptoms,²⁰ is independent of the unipolar-bipolar distinction, and provides direction for the appropriate choice of antidepressant medication.²¹

Melancholic depression belies the term depression in that it is a state of pathological hyperarousal. Intense anxiety is often focused on the self and takes the form of feelings of worthlessness and recollections of past transgressions, failures, and helplessness. As a corollary, melancholics are beset by dread about future prospects for so deficient a self. It matters little that their self assessments and emotional memories are discordant with the facts of their lives. Rather, their feelings of personal deficiency color and pervade thought and affect (reviewed in ⁵).

Patients with melancholic depression also manifest evidence of physiological hyperarousal such as hypercortisolism, suppression of the growth hormone and reproductive axes, insomnia (most often early morning awakening), and loss of appetite. Another consistent feature of melancholia is a diurnal variation in the severity of depressed mood, which is greatest early in the morning (reviewed in ⁵).

Although both atypical and melancholic depression are associated with dysphoria and anhedonia, atypical depression is in many ways the antithesis of melancholia. Atypical depression is associated with a disturbing sense of disconnectedness and emptiness, punctuated by brief emotional reactions to external circumstances. In contrast to melancholics, who seem to have ready access to negatively charged memories, patients with atypical depression often seem walled off from themselves. They may complain of a cognitive and mental weariness and avoid others, often with the sense that contact would be too demanding, tiring, and poorly received. Neurovegetative symptoms in atypical depression are the reverse of those in melancholia and consist of lethargy, fatigue, excessive sleepiness, increased food intake, weight gain, and depressive symptoms that worsen as the day progresses.²²

Only 25–30% of patients with major depression present with pure melancholic features while another 15–30% present with pure atypical features. Those with melancholic or atypical features show a much more severe course of illness than those with mixed neurovegetative features.²⁰ Recent data from identical

twin and family studies indicate that melancholic and atypical features are each heritable entities.²³ However, only a few studies of depression have stratified patients on the basis of clinical subtype.

We will first describe the stress system prior to our discussion of depression.

Phenomenology of the stress response

The acute response to danger consists of a relatively stereotyped series of physiological and behavioral programs that promote survival during threatening situations. Physiological changes include increases in heart rate and blood pressure, shifts in blood flow to the brain and to the stressed body site, and breakdown of tissue in the mobilization of fuel. In addition, there is inhibition of a repertoire of neurovegetative functions whose execution would be likely to diminish the likelihood of surviving a life threatening situation (eg feeding, sleep, sexual behavior, and the endocrine programs for growth and reproduction) (reviewed in ^{6,24}).

Fear-related behaviors predominate during stressful situations and are crucial for survival during emergencies. For this reason, an extensive circuitry for generating and modulating fear has evolved.²⁵ Depending on the context and constitutional factors (eg gender, stress system set point), fear leads to either defensive behavior that protects from harm or stimulates a struggle for survival. Speed and simplicity are essential, leading to a rapid deployment of simple, well-rehearsed behavioral and cognitive responses. At the same time, there is an inhibition of more complex, novel, or untested responses that require considerable time to assemble.²⁶

Consistency is also essential for surviving stressful situations and is most apparent in the inhibition of mood shifts from one state to the another. Thus, affect is often confined to a distressed, fearful mode. As noted, cognitive and behavioral repertoires are also relatively stereotyped during stressful situations. During the acute crisis, the mesolimbic dopaminergic reward system is stimulated to help maintain morale.²⁷ Different stressors activate different components of the stress system. The response to a physiological stressor like hypoxia may require the involvement of only hypothalamus and brainstem; structures such as the amygdala and prefrontal cortex must be recruited to effectively respond to somewhat more complex environmental danger.²⁸

The neurobiology of the stress response

The core stress system

For the purpose of this review, the core stress system consists of the (CRH) system and the locus ceruleus-norepinephrine (LC-NE) systems and their peripheral mediators, NE and cortisol. These systems play key roles in physiological responses to stressful situations, promoting arousal, essential for identifying a given situation as important, as well as for maintaining the limbic system and the cortex in states that most favor

survival during stressful situations. The core component also serves as a homeostat for the overall stress system, utilizing inputs from many areas in the brain and periphery in contributing to the modulation of the intensity and duration of the stress response.

The CRH system

CRH was first isolated as the principal hypothalamic hormone that releases corticotropin (ACTH), which in turn activates adrenocorticosteroid secretion. Over the years, a series of painstaking studies in rodents has established roles for CRH in the stress response other than that of HPA axis regulation. These include activation of the locus ceruleus, the sympathetic nervous system and the adrenal medulla, as well as inhibition of a variety of neurovegetative functions such as food intake, sexual activity, and the endocrine programs for growth and reproduction (reviewed in ^{3,6,24}). Extrahypothalamic CRH-containing neurons in the amygdala, though technically outside of the core stress system, also play a key role in the stress response by activating fear-related behaviors while inhibiting exploration (reviewed in ^{3,6,24}). Taken together, CRH in the rat participates in virtually the entire cascade of the physiologic and behavioral alterations occurring in response to stressors.

CRH-mediated glucocorticoid secretion has an abundance of adaptive and adverse effects. Acute glucocorticoid secretion during stress serves several roles, including enhancement of cardiovascular function and mobilization of fuel. Cortisol (along with CRH) also significantly contributes to the inhibition of programs for growth and reproduction via inhibition of the growth hormone and gonadal axes, as well as to feedback restraint upon an activated immune system.

For the most part, the adaptive advantages conferred by cortisol secretion during stress are limited to its acute rather than chronic release. Chronic cortisol excess is almost always deleterious and includes excessive fear, insulin resistance/visceral fat deposition and their many pro-atherogenic sequelae, osteopenia/osteoporosis, sarcopenia, inhibition of T helper-1 directed cellular immunity, and chronic suppression of the mesolimbic dopaminergic reward system.^{24,29} Glucocorticoid receptors are widely distributed in brain. Acutely, activation of glucocorticoid receptors located in the prefrontal cortex, hippocampus, amygdala, and the hypothalamus, inhibit the HPA axis. McEwen, Sapolsky, and their colleagues found that chronic activation of glucocorticoid receptors located in the hippocampus can damage hippocampal neurons containing glucocorticoid receptors, potentially leading to more severe hypercortisolism.³⁰ Not all glucocorticoid receptors transduce inhibitory effects. We found that activation of glucocorticoid receptors located in the central nucleus of the amygdala and the bed nucleus of the stria terminalis increase rather than decrease CRH mRNA. Glucocorticoids also raise CRH mRNA levels located in a distinct population of PVN neurons that send descending terminals to brainstem noradrenergic neurons.³¹

Corticotropin releasing hormone and its receptors in brain

In addition to the PVN CRH pathway to the median eminence, as noted, a separate pathway emanating from a distinct population of PVN CRH neurons descends for activation of brainstem noradrenergic neurons.³² An intrahypothalamic pathway for trans-synaptic release of CRH³³ was shown to inhibit the growth hormone³⁴ and reproductive axes³⁵ (in concert with cortisol) and to inhibit feeding³⁶ and sexual behavior.³⁷ An extrahypothalamic CRH system in the amygdala was subsequently shown to play a key role in classical fear conditioning.^{38,39} Thus, CRH was shown to participate in the behavioral, neuroendocrine, neurovegetative, and autonomic components of the stress response. The CRH receptor type 1 (CRHR 1) is widely distributed in brain to transduce its effects during stress and other situations.⁴⁰

While the CRHR-1 knockout mice show decreased anxiety,⁴¹ CRH type 2 receptor knockout mice show accentuation of arousal and anxiety, suggesting that this receptor may counter-regulate the anxiogenic effects mediated by type 1 receptor activation.^{42,43} Type 2 receptors also mediate diminished food intake. A CRH binding protein parallels CRH receptors in brain and functions as an endogenous CRH antagonist by complexing with CRH; its antagonism promotes arousal and diminishes feeding.⁴⁴

We have recently shown in rhesus macaques that the oral administration of a non-peptide CRH type 1 receptor antagonist (antalarmin) that penetrates the blood-brain barrier significantly inhibited stress-induced anxiety-like responses while promoting exploration (Figure 1). We also found that antalarmin significantly inhibited increases in plasma ACTH, NE, epinephrine and cortisol (Figure 1). These data indicate that CRH plays a tonic role in the comprehensive modulation of the stress response not only in rodents, but also in primates.⁴⁵ In rodent studies, we found that antalarmin not only blocked the expression of conditioned fear, but also its development and consolidation (Figure 2).⁴⁶ These data, if applicable to humans, suggest that a CRH antagonist could be helpful after an acute traumatic event or in preventing the adverse secondary CNS changes that occur during chronic stress (Figure 2). We have also found that antalarmin significantly reduces stress ulcer in the rat.⁴⁷ In the light of the important processes transduced by the type 1 CRH, many laboratories, including ours, are attempting to synthesize a small CRH antagonist with optimal lipophilicity that would be suitable as a PET ligand.⁴⁸ In an effort to develop such a ligand, in collaboration with Dr Kenner Rice, we have synthesized over 60 analogs of antalarmin.⁴⁹

The LC-NE system

The LC-NE system resides in the mid-pons and contains the highest concentration of noradrenergic cell bodies in the brain. A single LC neuron can have as

many as 100 000 nerve terminals and can innervate cells in several different portions of the brain. At normal firing rates, the LC is thought to increase the signal to noise ratio at disparate sites in brain by specifically enhancing responses to either excitatory or inhibitory stimuli. At faster LC rates, the general enhancement of signal to noise ratio decreases and the LC becomes the brain's alarm system. In addition, activation of the LC contributes to sympathetic nervous system and HPA axis stimulation. At the same time, LC activation inhibits the parasympathetic nervous system as well as neurovegetative functions such as feeding and sleep (reviewed in ⁵⁰).

During stress, the LC enhances the role of the amygdala and other structures involved in the encoding of aversively charged memories. Thus, the LC not only promotes survival during an acute crisis, but helps in preparing for subsequent dangers as well. Arnsten *et al* have recently found another important role of the LC-NE during stress, namely in the inhibition of the prefrontal cortex, thereby favoring rapid instinctual responses over more complex ones in the service of surviving acute life-threatening situations (see below ⁵¹).

Taken together, at fast firing rates, the LC, like the CRH system, plays a role in promoting arousal, inhibiting several vegetative functions, and biasing towards a loss of affective and cognitive flexibility.

The central role of the amygdala as a fear generator

Because fear is essential for surviving serious threats, the stress system must be capable of producing the experience of being afraid. The amygdala is a key structure that transforms experiences into feeling.²⁵ To accomplish this task, the amygdala provides working memory with information about whether something is good or bad and, along with the core stress system, activates disparate arousal centers to maintain focus upon the current danger.²⁵ Like the core stress system, the amygdala evolved relatively early compared to higher cortical centers.

The amygdala is responsible for acquiring and storing classic fear conditioned responses that can be immediately mobilized even though they remain outside of conscious awareness.²⁶ Because the amygdala cannot store complex, explicit, aversively charged emotional memories, it relays them to areas such as the hippocampus and striatum for retrieval during subsequent emergencies.⁵²

Like the core stress system, the amygdala is thought to inhibit key functions of the prefrontal cortex. The amygdala also stimulates hypothalamic CRH release and brainstem autonomic centers resulting in increased HPA and LC activity. These core stress system mediators not only confer adaptive physiological advantages, but are also thought to encode visceral responses that provide bodily feedback as part of the overall affective experience. In addition, both norepinephrine and cortisol significantly enhance the relay and encoding of aversively charged emotional memories from the amygdala to elsewhere in brain.²⁶ Taken

Nonpeptide CRH Type-1 Receptor Antagonism *in vivo*

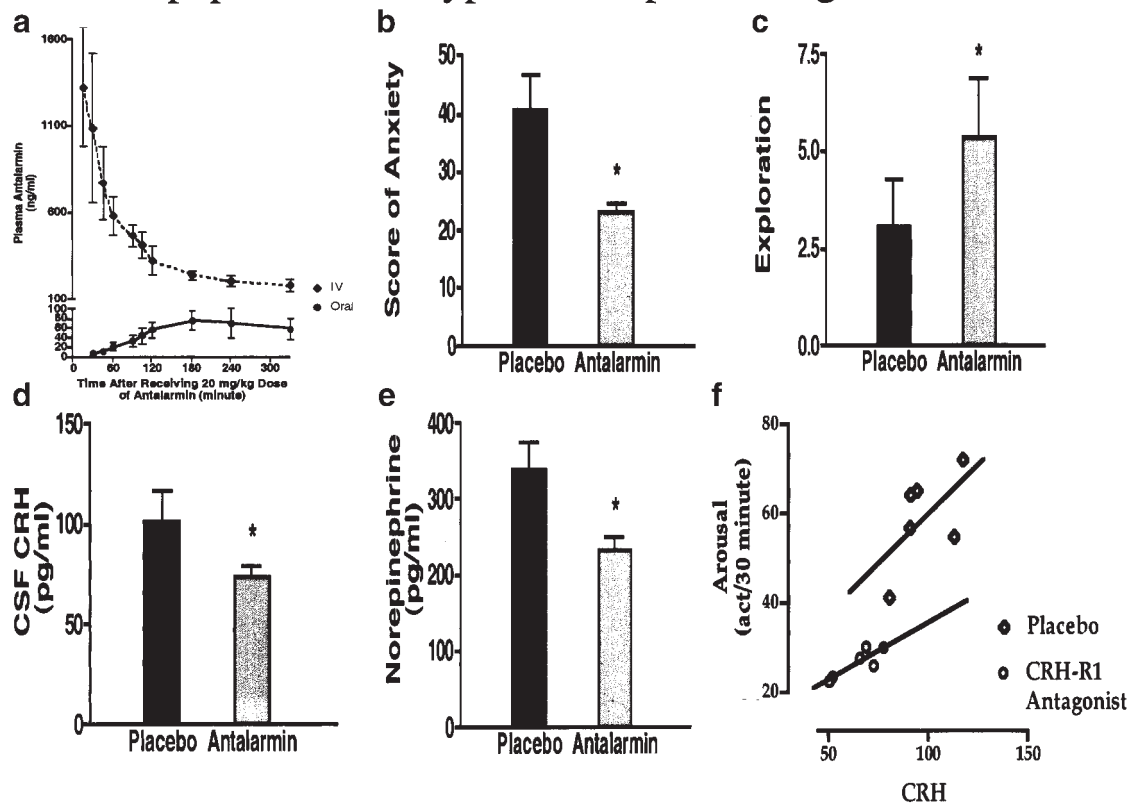


Figure 1 Effects of antalarmin on behavior and neuroendocrine responses in rhesus macaques. (a) pharmacokinetics in plasma; (b) effects on anxiety; (c) effects on exploration; (d) effects on CSF CRH; (e) effects on plasma norepinephrine; (f) antalarmin effects on dose response curve for arousal vs CSF CRH. At a given level of CSF CRH, arousal levels are lower for antalarmin treated macaques. From Habib *et al. Proc Natl Acad Sci* 2000; **97**: 6079–6084.

together, there are multiple feed forward loops among the amygdala, the hypothalamus, and brainstem noradrenergic neurons. Thus, the stress system contains the elements for a sustained and powerful stress response.

The prefrontal cortex

The prefrontal cortex accounts for approximately one-third of human brain volume. In many respects the prefrontal cortex exerts cognitive, behavioral, affective, and physiological responses that are the virtual antithesis of those set into motion during stress. At the same time, the prefrontal cortex and the stress system inhibit each other's activity.^{53–55}

The dorsolateral prefrontal cortex plays key roles in complex, time consuming planning and problem solving (reviewed in^{53–55}) in part, by sequentially scheduling complex tasks by switching focused attention between tasks.⁵⁶ The dorsal prefrontal cortex also provides a perspective on whether a given task is proceeding satisfactorily.⁵⁶ In contrast, successful responses to danger depend upon simplicity and speed, generally antithetical to complex planning and problem solving. Indeed, Arnsten *et al* have shown that an activated LC-NE inhibits many key functions of the prefrontal cortex.^{51,57} Therefore, optimal functioning of the dorso-

lateral prefrontal cortex requires a relatively quiescent stress system.

The progression from dorsolateral to ventromedial prefrontal cortex is associated with a progressive shift from attention/cognitive matters to the modulation of affect, neuroendocrine regulation, and autonomic activity. The ventral prefrontal cortex (especially the orbital cortex) promotes extinction of responses to stimuli that are not reinforced, including the extinction of conditioned fear responses encoded in the amygdala.^{51,57–60} Humans with lesions of the orbital cortex, like endangered individuals, seem driven and disinclined or unable to shift intellectual strategies and affect on the basis of changing demands.^{51,57–60} Flexibility in affect and cognition requires not only an activated prefrontal cortex, but also an inhibited stress system (and vice versa).

Another component of the ventral prefrontal cortex, the subgenual prefrontal cortex, participates in determining whether a given situation is likely to result in punishment or reward and in the adjustment of affect based on changes in the environment.⁶¹ This capacity contrasts to the unconditional maintenance of fear during stress, even if there is preliminary indication that the danger is about to subside. Similarly, it

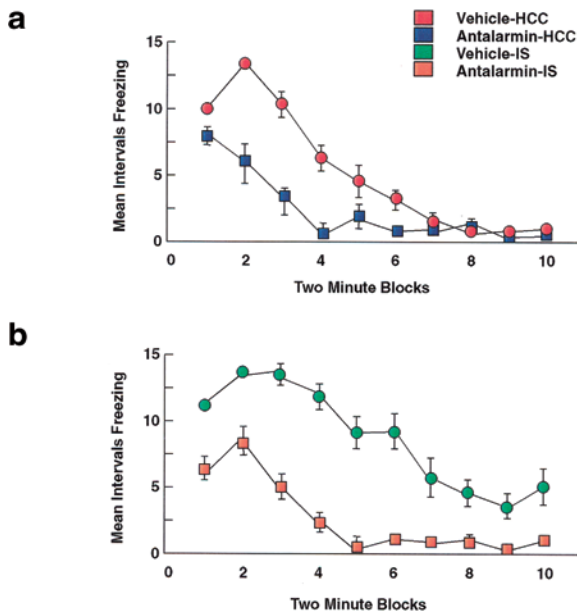


Figure 2 Antalarmin inhibits both the (a) development and (b) expression of conditioned fear. Antalarmin given both before and after conditioning produces a greater effect than either. From Deak *et al.* *Endocrinology* 1999; **140**: 79–86.

is adaptive during stress to expect the worst. An effective prediction about whether punishment or reward is on the way requires not only an intact prefrontal cortex, but also lack of interference by an activated stress system.

The ventral and prefrontal and subgenual prefrontal cortex also exert cortical inhibition upon the HPA axis and the sympathetic nervous system. Humans with lesions that include the anterior cingulate gyrus and/or subgenual prefrontal cortex show exaggerated autonomic and endocrine responses even when in apparently non-stressful situations.⁵⁶ In the rat, bilateral lesioning of the infralimbic region disinhibits the HPA axis.⁶² Further study in the rat revealed that lesioning of the left infralimbic cortex disinhibited the core stress system, while lesioning of the right resulted in subnormal activity of the HPA axis and the LC-NE systems.⁶² Thus, in the rat, the left prefrontal cortex inhibits the right. We have found evidence of the lateralization of neuroendocrine function as well.⁶³ It is of potential interest that the most replicated neuroimaging results in depression are those showing abnormalities in the left amygdala and left subgenual prefrontal cortex. Figure 3 provides a schematic diagram of the various reciprocal positive reinforcing loops among stress system components, hypothesizing defects on the left for melancholia (see below).

Mayberg has advanced data that nicely illustrate bidirectionally the reciprocity between cortical and subcortical sites and suggest that the reciprocity between these sites is immediate and obligatory.⁶⁴ The capacity of the stress system to inhibit prefrontal cortex function is but one of several mechanisms that insure a vigorous and sustained stress response. Figure 3 schematically

illustrates the many potential positive feedback loops that emerge during activation of the stress response in which each component activates the other.

Role of the stress system in the pathophysiology of melancholic and atypical depression

We shall next discuss the role of the stress system in the clinical, biochemical, and structural alterations documented in patients with major depression. We shall begin with core system abnormalities and then review abnormalities of amygdala and prefrontal cortex as well. We focus not only on the role of stress system dysregulation in the classic symptoms of depression, but also on the long-term medical consequences of this disorder.

The hypercortisolism of depression is one of the most frequent findings in biological psychiatry, though many papers cited normal cortisol levels as well. It is generally accepted that hypothalamic CRH is elevated in depression. We were the first to report a CRH abnormality in patients with depression. In our first original article, we showed that hypercortisolemic patients had significantly blunted plasma ACTH response to ovine CRH, in association with a substantial cortisol response.⁶⁵ These data were subsequently replicated by Holsboer and colleagues, and were published in a letter.⁶⁶ These data indicated that the hypercortisolism of depression appropriately restrained the HPA axis, suggesting a defect above the hypothalamus. Thus, the higher the basal cortisol, the lower the plasma ACTH response. The substantial cortisol response to a blunted ACTH response indicated that the adrenals had been chronically overstimulated, and therefore hypertrophied and hyperresponded to ACTH. Our studies in patients with Cushing's disease, a peripherally (pituitary) mediated form of hypercortisolism, helped substantiate the central origin of the hypercortisolism of major depression. In contrast to patients with major depression, patients with Cushing's disease showed profound ACTH and cortisol responses to CRH, indicating that the pituitary itself was resistant to cortisol negative feedback. Our subsequent studies further confirmed that the hypothalamic component of Cushing's disease responded normally to glucocorticoid negative feedback. The pronounced differences of the responses to CRH in depression and Cushing's disease, based on their distinct pathophysiology, proved to be clinically useful in the often difficult differential diagnosis between major depression with pronounced hypercortisolism and early or mild Cushing's disease.⁶⁷

Many other lines of evidence support a role for the hypersecretion of CRH in the pathophysiology of hypercortisolism. Nemeroff *et al* found that CRH receptor numbers were reduced in frontal cortex in post mortem samples taken from patients who had died by suicide.⁶⁸ Nemeroff also found that CSF CRH levels in depressed patients⁶⁹ were elevated and later showed that CSF CRH levels in patients fell significantly after treatment.⁷⁰ In our group, DeBellis found that fluoxetine significantly lowered CSF CRH levels when

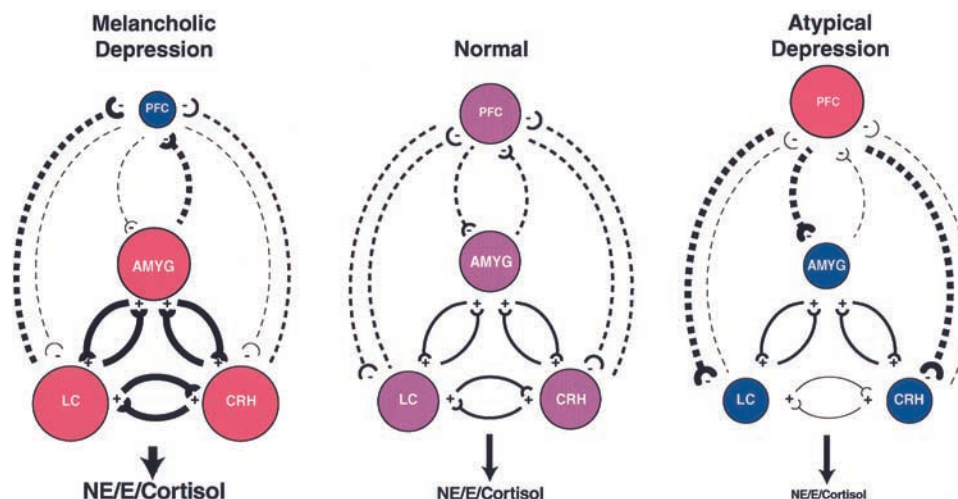


Figure 3 Schematic diagram of the interrelation of stress system mediators and circuitries in melancholic and atypical depression. (middle) Normal. In the absence of stressful stimuli, the stress system is not quiescent, but rather resides in a dynamic state of bidirectional interactions among stress mediators. Such a homeostatic equilibrium can react flexibly to a range of different stimuli that may preferentially affect one component over another. Available data in primates suggest that under ordinary circumstances: (1) the prefrontal cortex inhibits the amygdala, HPA axis, and LC-NE system; (2) an activated amygdala inhibits the prefrontal cortex and stimulates both the HPA axis and the LC-NE. In the reverse direction: (3) the LC-NE activates the amygdala and HPA axis and inhibits the prefrontal cortex; (4) the HPA axis activates the LC-NE and the amygdala. Dotted lines inhibitory, solid lines excitatory. Schematically, in the normal state, the relative strength of each component is similar, denoted by circles of identical diameter. (left) Melancholic depression can be conceptualized as a prolonged and intensified stress response that does not yield to its ordinary counter-regulatory restraints. The net effect is a pronounced shift in equilibrium with the following results: (1) diminished activity of the prefrontal cortex; (2) activation of the amygdala; (3) activation of the core stress system. The primary defect could arise from any of the structures pictured in the schematic diagram or circuits in which they participate. Note reciprocal relations between prefrontal cortex and subcortical stress components. Also note that the amygdala, LC, and CRH system are all excitatory to one another so that an increase in the activation of one component could set off a reverberate sequence of further activations unless overtaken by inhibitory stimuli. Similarly, the prefrontal cortex and the components of the stress system exhibit bi-directional inhibition on one another. (right) Atypical depression can be conceptualized as a state of stress system hypoactivity that has yielded too readily to its counter-regulatory restraints. The net effect is a pronounced shift in equilibrium with hypoactivity of each of the components of the stress system. Theoretically, the prefrontal cortex could be disinhibited or primarily hyperactive. Abbreviations: PFC, prefrontal cortex; AMYG, amygdala.

depressions remitted.⁷¹ In addition, we found that the chronic administration of imipramine to healthy volunteers produced effects incompatible with a central downregulation of the HPA axis.⁷² CSF CRH. Finally, in experimental animals, we showed that the chronic, but not acute, administration of imipramine significantly reduced CRH mRNA levels while significantly increasing the mRNA levels of the type I glucocorticoid receptor in the hippocampus, thought to be an important element in the feedback inhibition of the HPA axis.⁷³

In a study of the 30-h pattern of CSF CRH levels in severely depressed inpatient melancholic subjects and controls, we found inappropriately 'normal' integrated 30-h CSF CRH concentrations despite significant hypercortisolism and around-the-clock elevations of CSF NE⁷⁴ (Figure 4). Because the overall pool of CSF CRH and plasma ACTH levels are glucocorticoid suppressible,⁷⁵ we previously suggested that quantitatively 'normal' CSF CRH and plasma ACTH levels in the face of hypercortisolism are, nevertheless, inappropriate for the patients' degree of hypercortisolism.⁷⁶ Our reasoning was as follows: we compared levels of CSF CRH in patients with depression associated with Cushing's

disease (a pituitary disorder), who had matching degrees of hypercortisolism. We found extremely low levels of CSF CRH in our patients with Cushing's disease, whose CNS was normal but in whom very high levels of pituitary driven cortisol bombarded the hypothalamic CRH system, profoundly suppressing it.⁶⁷ In contrast, in a group of patients with major depression associated with hypercortisolism of similar magnitude to the group of patients with Cushing's CSF CRH levels were substantially and significantly higher in depressed patients than in those with Cushing's disease. Thus, cortisol itself has a highly significant suppressive effect on the overall levels of CSF CRH. In contrast, CSF levels in the depressed patients were not suppressed at all. The failure of hypercortisolism to suppress CSF CRH levels in depressed patients suggests either resistance to glucocorticoid negative feedback at several potential sites or an overdriven HPA axis whose drive overcomes normal glucocorticoid feedback, a possibility that we favor. This formulation is compatible with the finding that the significant negative correlation between CSF CRH and plasma cortisol found in controls was lost in patients with melancholic depression⁷⁴ (Figure 5). We had previously found that

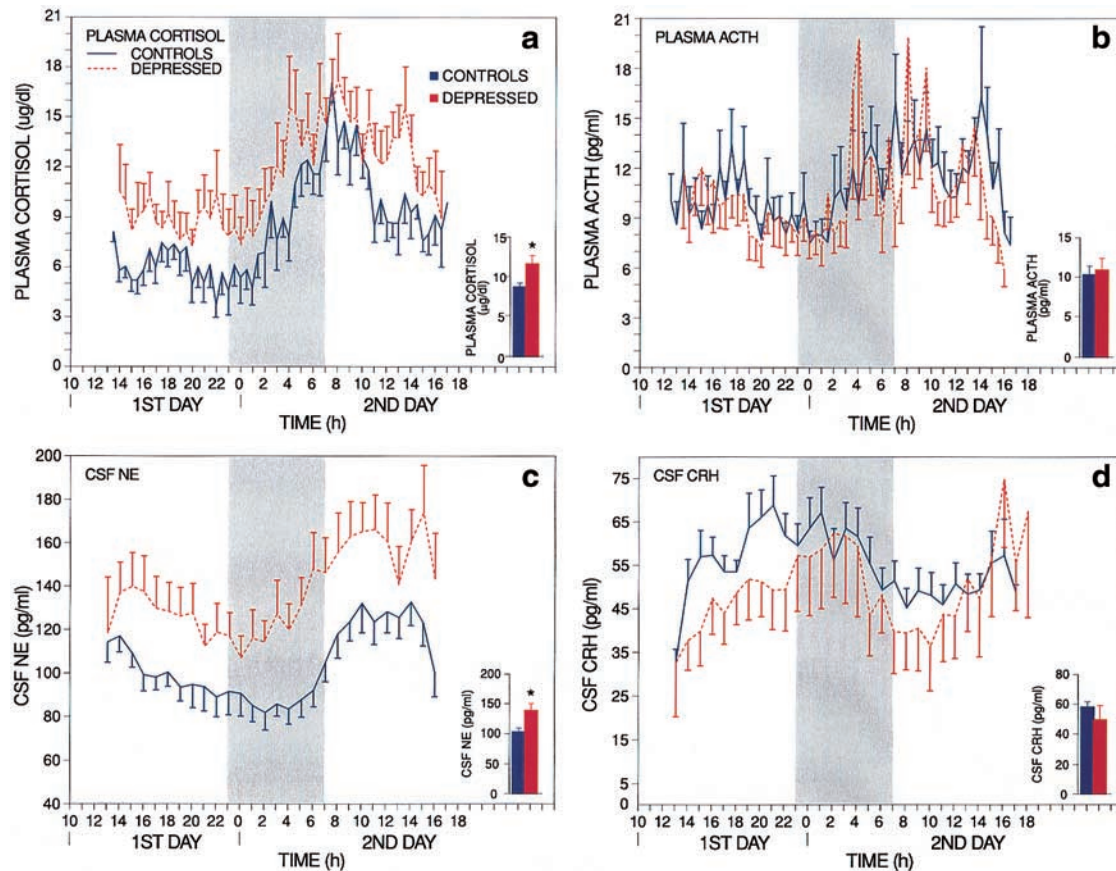


Figure 4 Thirty hour levels of CSF CRH, CSF norepinephrine, plasma ACTH and plasma cortisol. Diurnal curves of (a) plasma cortisol, (b) plasma ACTH, (c) CSF NE and (d) CSF CRH levels (mean $\pm$ SE) in 14 healthy volunteers and 10 patients with major depression, melancholic type. Curves are resultant from the averaged measurement per time point across a group of subjects using the cropped hormonal series. The shaded area represents lights off (2300–0700 h). In the right corner insets under each pair of curves, the bar graphs represent the average of the mean value for each series of hormonal measurements (mean $\pm$ SE). * $P < 0.02$. Despite around-the-clock increases in plasma cortisol and CSF NE levels, CSF CRH and plasma ACTH are similar to those in controls, though inappropriately high for the degree of hypercortisolism. Note that the diurnal rhythms for plasma cortisol and CSF NE are virtually superimposable. From Wong *et al. Proc Natl Acad Sci* 2000; **97**: 325–330.

CSF CRH levels were normal in a hypercortisolemic group of patients with melancholia, utilizing single measurements of CSF CRH, while Geraciotti found significant decrements in CSF CRH in a group of eucortisolemic depressed patients (see below).

The interpretation of the meanings of CSF CRH in depression is complicated by the fact that the PVN-median eminence component is restrained by glucocorticoid negative feedback. Glucocorticoids, on the other hand, increase CRH mRNA levels in the amygdala, bed nucleus of the stria terminalis, and in the PVN CRH pathway descending to brainstem noradrenergic neurons. We have found that lesioning the PVN in the rat decreases CSF CRH by 50–60% (Mamalaki E, unpublished observations). Thus, activations of amygdala CRH neurons and of those that descend from the PVN to the brainstem would be neutralized by the potent suppressive effects of glucocorticoids on the CRH involved in the HPA axis. Given the various permutations and combinations of multiple sites secreting CRH into the CSF, we would not be surprised by findings of increased CSF CRH levels in

patients vs controls. The pathophysiologic meanings of the two are virtually identical.

Although there are many intriguing lines of information implicating CRH in the pathophysiology of major depression, especially melancholia, it should be emphasized, that this has by no means been definitively substantiated, but merely supported by circumstantial evidence. The availability of a CRH type 1 antagonist that crosses the blood–brain barrier should provide further important information about the role of CRH in depression.

The locus ceruleus norepinephrine system

Studies of biological factors in major depression have largely relied on serendipitous discovery of antidepressants and the determination of their mechanisms of action. The most important hypothesis to emerge from this work was the catecholamine hypothesis of depression.⁷⁷ This hypothesis was based on the assumptions that pharmacologic depletion of NE by reserpine apparently induced major depression, while

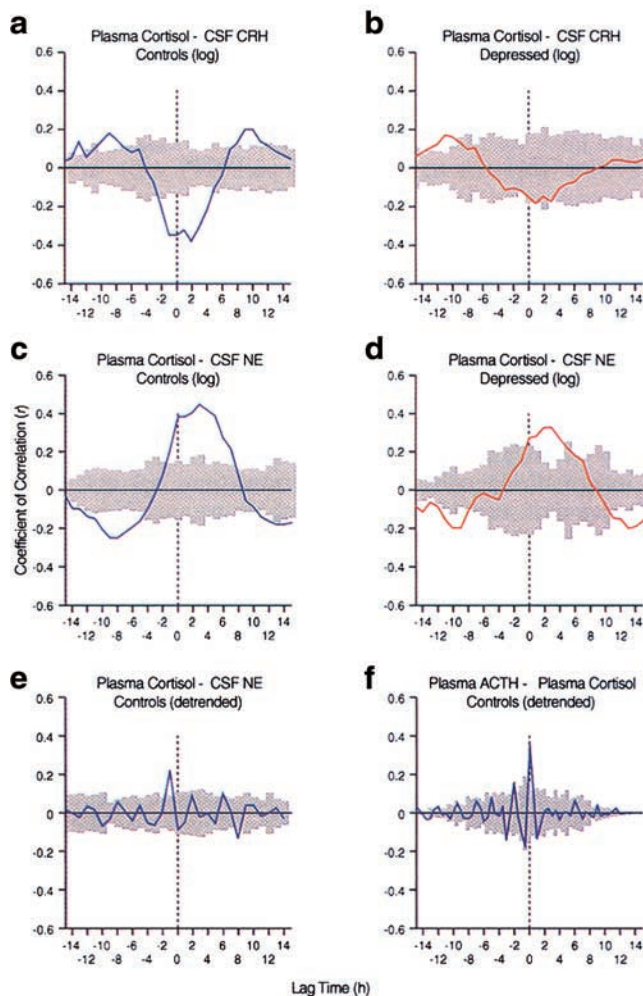


Figure 5 Cross correlations of the 30-h levels of CSF CRH and cortisol and between CSF NE and cortisol. Cross correlation analysis of the mean coefficients of variation between CSF CRH and plasma cortisol (a and b), and between CSF NE and plasma cortisol (c and d). Note the negative correlation between cortisol and CRH in controls which is lost in patients. A positive correlation exists between NE and cortisol during standard cross correlational analysis and in the detrended analysis as well (e, f). The detrended CSF analysis corrects for the effect of diurnal variation and is an index of rapid changes in hormone levels between CSF NE and plasma cortisol level. Note that the positive detrended correlation between CSF NE and plasma cortisol is almost as robust as that between plasma ACTH and plasma cortisol. From Wong *et al. Proc Natl Acad Sci* 2000; **97**: 325–330.

apparent pharmacologic augmentation of noradrenergic activity by MAO inhibitors and NE uptake inhibitors (tricyclic antidepressants) exerted antidepressant effects.⁷⁸ By positing that depression could be caused by a deficiency of NE rather than only by early psychological trauma or a lifetime of adverse events, the catecholamine hypothesis served as a major impetus for the emergence of modern biological psychiatry.

Although the original catecholamine hypothesis of major depression stated that a deficient NE delivery to

its receptors in the CNS was one of the main causes of depression,⁷⁷ studies of NE or its metabolites in CSF, plasma, or urine, or of components of the noradrenergic system in post-mortem brain samples, reported indices suggestive of decreased,^{79–96} normal,^{97–105} or increased^{106–110} delivery of NE to its intended receptors in the CNS or periphery. It should be noted that almost all of the prior studies of CSF NE or its metabolites in depressed patients were based on single time points. Moreover, neither *in vivo* nor post mortem studies stratified patients on the basis of depressive symptomatology of melancholic or atypical subtype.

In an attempt to clarify *in vivo* central noradrenergic function in major depression, we studied a group consisting only of very severely, drug-free depressed melancholic patients who were to receive ECT for the treatment of their depression. Via an indwelling lumbar drain, we measured CSF CRH and NE 30 consecutive hours. We also took half-hourly samples of plasma ACTH and cortisol. We found unequivocal evidence of a pronounced central hypernoradrenergic state in melancholic patients. CSF NE levels were elevated around the clock, including during sleep⁷⁴ (Figure 4c). Although there has been debate about the origin of CSF NE, Goldstein *et al* found that patients with the Shy-Drager syndrome, a neurodegenerative disease that features loss of central noradrenergic cells but intact post-ganglionic sympathetic nerves,¹¹¹ have a dissociation between normal plasma NE and DHPG levels and low CSF NE and DHPG levels (D Goldstein, unpublished observations). These data indicated that the hypernoradrenergic state of depression was not related to the conscious distress of the disorder.

Plasma cortisol levels were also significantly increased. Melancholic patients, like controls, showed diurnal rhythms of CSF NE and plasma cortisol levels that were virtually superimposable and positively correlated (Figure 5). These data suggest the hypothesis that cortisol stimulates centrally directed NE, and are compatible with our *in vitro* finding that NE stimulates CRH from hypothalamus, subsequently replicated by Itoi and colleagues.^{24,112}

In this regard, a post mortem study by Radesheer *et al* of brains taken from depressed patients who had committed suicide showed a significant increase in hypothalamic neurons expressing CRH that was predominantly found in neurons sending descending projections to brainstem noradrenergic nuclei¹¹³ (Figure 6). These data suggest that a specific, relatively small hypothalamic CRH pathway which just goes to the brainstem may play a disproportionate role in the pathophysiology of melancholia and implicate a particularly important way in which CRH and NE may interact in this disorder. As noted earlier, glucocorticoids increase CRH mRNA levels in the separate PVN-containing population of CRH neurons that descend to brainstem noradrenergic neurons. Therefore, these data suggest a specific way in which glucocorticoids can activate a CRH pathway which then goes on to activate brainstem noradrenergic neurons, providing another

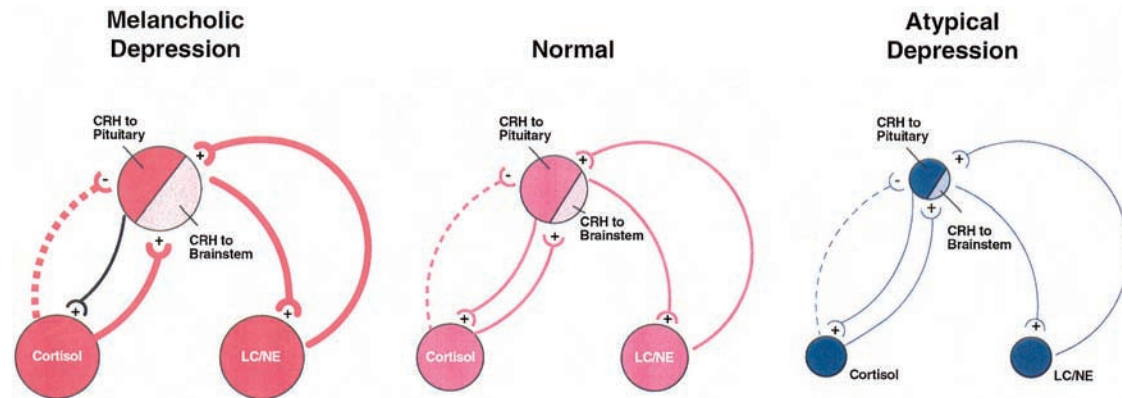


Figure 6 A specific PVN CRH pathway to brainstem noradrenergic nuclei independent of the HPA axis. Post mortem studies in patients who had been diagnosed with major depression reveal a significant increase in hypothalamic CRH-containing neurons. Surprisingly, this increase was much more pronounced in hypothalamic CRH-containing neurons that send descending projections to brainstem noradrenergic nuclei. The fact that glucocorticoids seem to activate rather than restrain this pathway introduces another context for a positive feedback loop in which an activated HPA axis leads to increased CRH secretion, which in turn activates brainstem noradrenergic nuclei. This feedback loop may contribute to the pronounced hypernoradrenergic state seen in melancholic depression as well as the positive correlation we found between CSF NE and plasma cortisol levels seen in both patients and controls. The postulated activating effects of glucocorticoids upon hypothalamic CRH containing neurons that send descending fibers to brainstem noradrenergic nuclei establishes yet another positive feedback loop within the stress system and in melancholic depression.

context for mutual reverberatory loops between CRH, NE, and cortisol. These relationships in melancholic depression are detailed in Figure 3.

Re-interpretation of neuropharmacological data of relevance to depression

Scientists were initially convinced that norepinephrine uptake blockers and MAO inhibitors enhanced noradrenergic function by either preventing the removal of NE from the synaptic cleft⁷⁸ or by interfering with its enzymatic degradation. However, the elegant work of Weiss and others has shown that tricyclic antidepressants, MAO inhibitors, and specific serotonin uptake inhibitors consistently decrease the firing rate of the LC during stress.¹¹⁴

Although the purported capacity of reserpine to induce depression played a prime role in the original catecholamine hypothesis of depression, a carefully-written review of the cases of reserpine-induced depression suggests that, in retrospect, most patients may have experienced a neuroleptic like syndrome consisting of sedation, hyperphagia, apathy, and Parkinsonism.¹¹⁵

It should be emphasized that we do not believe that all melancholics have activated noradrenergic secretion. The pathophysiology of this state is, of course very complex and influenced by multiple genes. There may be many melancholic patients who have normal noradrenergic function but combined abnormalities in other genes in the context of adverse environmental factors that lead to melancholia. It is also, of course, clear that norepinephrine is not the only or principal neurotransmitter involved in the pathophysiology of major depression. Norepinephrine and serotonin uptake inhibitors each exert effects on

both systems, suggesting an important role for serotonin as well.

Over a dozen 5HT receptors have been identified. In some cases, multiple receptors are found on the same neuron that exert antithetical effects on cell firing. In the midst of this diversity and complexity, the hypothesized role for 5HT in the pathophysiology of depression is based largely on data showing that effective antidepressants of all classes (including NE uptake inhibitors) increase the release of 5HT.¹¹⁶ In addition, effective antidepressants, including specific norepinephrine as well as serotonin uptake inhibitors, increase the density of post-synaptic 5HT_{1a} receptors and decrease the density of 5HT_{2a} receptors.¹¹⁷ As a corollary, post-synaptic 5HT_{1a} are reduced in the brains of suicides, while post-synaptic 2a receptors are increased in suicide post-mortem brains.¹¹⁸ The interdependence of the LC-NE and serotonergic systems is illustrated by the fact that activation of 5HT_{1a} receptors leads to a decrease in LC firing¹¹⁹ and in the density of cortical beta adrenergic receptors, while activation of 5HT_{2a} receptors increases the LC firing rate.¹²⁰

The confluence of long-term activation of the CRH and noradrenergic systems in depression, in association with glucocorticoid hypersecretion, is a highly pathologic state that could readily produce the profound hyper-arousal and anxiety that occurs in melancholic depression. The capacity for components of the CRH and NE systems to activate one another, to lead to glucocorticoid excess, and for key components of each to respond (eg the amygdala CRH neurons) positively to glucocorticoids, establishes the context for a pernicious cycle of stress-mediator activation that can be exceedingly difficult to break (Figure 3). Excessive secretion of norepinephrine and cortisol, regardless of

the primary cause, could intensify this pathophysiological picture in several ways. By activating the amygdala and inhibiting the medial prefrontal cortex, norepinephrine would promote well rehearsed rather than novel programs of behavior and accentuate the activity of the amygdala. Glucocorticoid excess could set into motion several vicious cycles, including damage to hippocampal glucocorticoid responsive neurons that restrain the HPA axis, activation of the amygdala and extra-amygdala sites involved in conditioned fear and declarative emotionally-laden memories (that would in turn lead to more hypercortisolism), and activation of descending hypothalamic CRH pathways to further potentiate brainstem noradrenergic activity.

To support a role for glucocorticoids accelerating this vicious cycle, are the data of Schatzberg's on the several-day glucocorticoid antagonist administration in patients with psychotic depression. RU 486 induced a rapid decrease in depressive symptoms of at least 50% in the majority of his patients. This study lays the groundwork for the potential use of RU 486 as a rapidly acting agent for ameliorating very severe depressive syndromes that require immediate intervention (Belanoff *et al* in press, *PNAS*).

Neuroimaging studies of stress system components in major depression

Neuroimaging studies in patients with major depression reveal changes at local synaptic sites in several areas, most notably the amygdala and prefrontal cortex. Such regional abnormalities will ultimately provide the basis for the construction of models that place these abnormalities in the context of the various cycles in which these structures partake.

Patients with major depression show increased cerebral blood flow and metabolism in the amygdala.¹²¹ Activation in the left amygdala persisted after recovery from depression. During depression, amygdala activation correlated positively with depression severity and baseline plasma cortisol levels.¹²¹ The latter finding is of interest in the light of the fact that the amygdala activates the HPA axis.³¹ Glucocorticoids in turn, accentuate the amygdala CRH system.¹²² A recent study found that neural activity in several 5-HT-related brain areas, eg dorsal raphe, habenula, septal region, amygdala, and orbitofrontal cortex, covaried significantly with plasma levels of tryptophan and ratings of depressed mood. Antidepressant-treated patients who relapsed upon tryptophan depletion had higher baseline amygdala metabolism than similar subjects who did not relapse.

A series of studies in patients with major depression have reported significant decreases in activation of the dorsolateral prefrontal cortex and significant increases in ventral prefrontal and paralimbic structures.¹²³ Higher depression ratings correlated negatively with the activity of left dorsolateral prefrontal cortex, while anxiety levels were positively correlated with paralimbic system activity. Successful treatment of depression was associated with inhibition of overactive paralimbic

regions and normalization of hypoactive dorsolateral prefrontal cortex sites.¹²⁴ Thus, major depression seems associated with hypoactivity of cortical structures and a corresponding hyperactivity of paralimbic/subcortical loci.

A key finding that has been well replicated is that of a significant loss of volume in the left subgenual prefrontal cortex, an area that is closely connected to the amygdala and that contributes to the inhibition of the HPA axis and sympathetic nervous system.¹²⁵ These patients had predominantly melancholic depression (W Drevets, personal communication). Scanning and examination of post mortem brain samples taken from patients who had committed suicide revealed a 40% decrease in the volume of the left sub-genual cortex. It is of interest that the lateralization found in patients with depression is compatible with data in the rat showing that lesioning of the left infralimbic cortex causes activation of the HPA axis and of sympathetic function, while lesioning of the right produced a decrement in the activity of these systems. These data indicate that the left infralimbic region inhibits the right.¹²⁶ We therefore postulate that the left-sided defect in melancholic depressed patients leads to hyperactivity of both the amygdala and core stress system components. In patients with atypical depression, however, the left could be hyperactive or hypertrophied, leading to excessive restraint of the right and hypoactivity of core stress system components. Thus, in patients with this subtype of depression, a primary defect in the right side may emerge, in contrast to that seen in melancholia (Figure 7).

Long-term medical consequences of melancholic depression

Patients with major depression show a doubling of the mortality rate at any age, independent of suicide.^{10,127} Premature ischemic heart disease is likely to play an important role, and the relative risk for clinically significant coronary artery disease in patients with major depression is 2.0 or more in studies that independently controlled for risk factors such as smoking and hypertension.^{10,127} Figure 7 details the potential mechanisms for premature ischemic heart disease that includes a vicious spiral between insulin resistance and increased visceral fat, potentially leading to hypertension, dyslipidemia, hypercoagulation, and enhanced endothelial inflammation.^{128,129} Increased sympathetic outflows seen in both our severely depressed inpatients and less severely depressed outpatients also further add to cardiac risk in several other ways. Norepinephrine is well known to promote insulin resistance,¹³⁰ left ventricular hypertrophy,¹³¹ and increases in myocyte growth, arteriolar and ventricular remodeling,^{132,133} blood volume and blood viscosity.¹³⁴ In addition, NE also activates platelets, cytokine release and is arrhythmogenic¹³⁵ (Figure 7).

We have also shown that as many as 40% of premenopausal women (average age 41) with severe affective disorder have peak bone density that is two

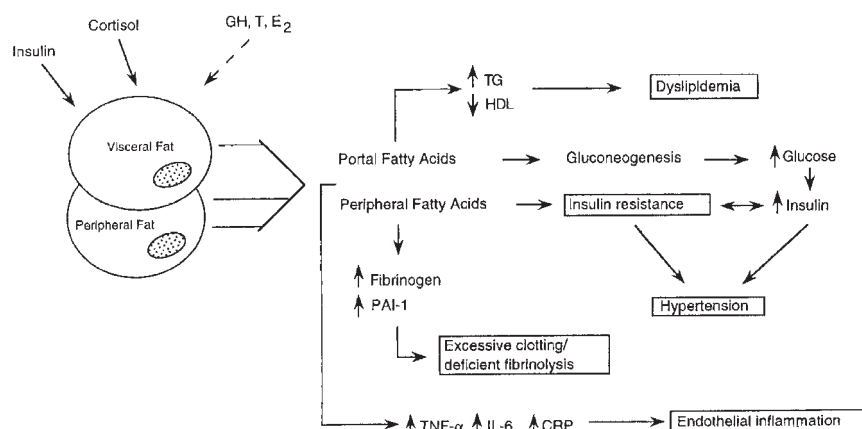


Figure 7 Factors in major depression that promote susceptibility to heart disease. Hypercortisolism and a deficiency of sex steroids and growth hormone each contribute to increases in the visceral fat mass, leading to increases in both portal and peripheral free fatty acids. Hypercortisolism and the increases in portal and peripheral free fatty acids both contribute to insulin resistance, which exacerbates the increase in visceral fat mass and promotes activation of the sympathetic nervous system and hypertension. Elevated portal free fatty acids lead to dyslipidemia associated with increased triglycerides (TG) and decreased HDL cholesterol. Increased portal and peripheral free fatty acid levels also promote endothelial inflammation through increases in tumor necrosis factor α (TNF- α), interleukin 6 (IL-6), and C-reactive protein (CRP). Peripheral free fatty acids increase the hepatic production of fibrinogen and the level of plasminogen activator inhibitor 1, leading to increased clotting and deficient fibrinolysis. GH denotes growth hormone; T, testosterone; E₂, estradiol; PAI-1, plasminogen activator inhibitor. From Gold and Chrousos. *Proc Assoc Am Phys* 1999; **111**: 22–34.

standard deviations or (20%) below their peak¹³ (for biopsy sample in a 40-year-old woman, please see Figure 8). We have also shown that these women show an almost 40% incidence of premature osteoporosis at either the hip or spine, which usually occurs in the mid-to-late twenties.¹³ Ordinarily, bone mineral density does not fall 20% below peak density until women are in their 60s. For every 10% loss below peak density, the fracture rate doubles.¹³⁶ For 40-year-old women, this is not a great risk. However, for 40-year-old women who were already 20% below peak density, this means that they have lost 1.5–2% per year since attaining peak bone density at 28–30. At age fifty, they could potentially have bone mineral density that is 35% below peak density and enter the menopause with already very compromised bones.¹³⁶ It is of interest that in our depressed women, in contrast to the usual presentation of osteoporosis or osteopenia, the greater loss of bone mineral density was at the hip rather than at the spine. We must emphasize that this degree of bone loss is likely to reflect the fact that our patients had severe affective illness. Thus, large studies of patients with major depression in outpatient settings are likely to find a lower incidence of osteopenia/osteoporosis.

Many factors could contribute to this loss of bone mineral density in women with past or current depression. Hypercortisolism is an obvious potential cause.¹³⁷ In patients given glucocorticoids, maximal bone loss occurs at 3–4 months after treatment.^{138,139} Since depressed, hypercortisolemic patients have glucocorticoid concentrations that are often equivalent to a patient receiving 10 mg of prednisone for 4 months or longer, the loss of bone in hypercortisolemic depressed patients can be quite severe. These data make a clear plea for the early and effective treatment of melan-

cholic depression. In addition to hypercortisolism, other factors could also contribute to bone mineral density loss in women with depression, including suppression of the growth hormone and gonadal axes. The hypersecretion of NE in patients with melancholia could also contribute to bone loss via activation of the secretion of IL-6. In postmenopausal women, it is IL-6 hypersecretion in the face of falling estrogen levels that is primarily responsible for post-menopausal osteoporosis.

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A series of studies in patients with major depression have reported significant decreases in activation of the dorsolateral prefrontal cortex and significant increases in ventral prefrontal and paralimbic structures.¹⁴¹

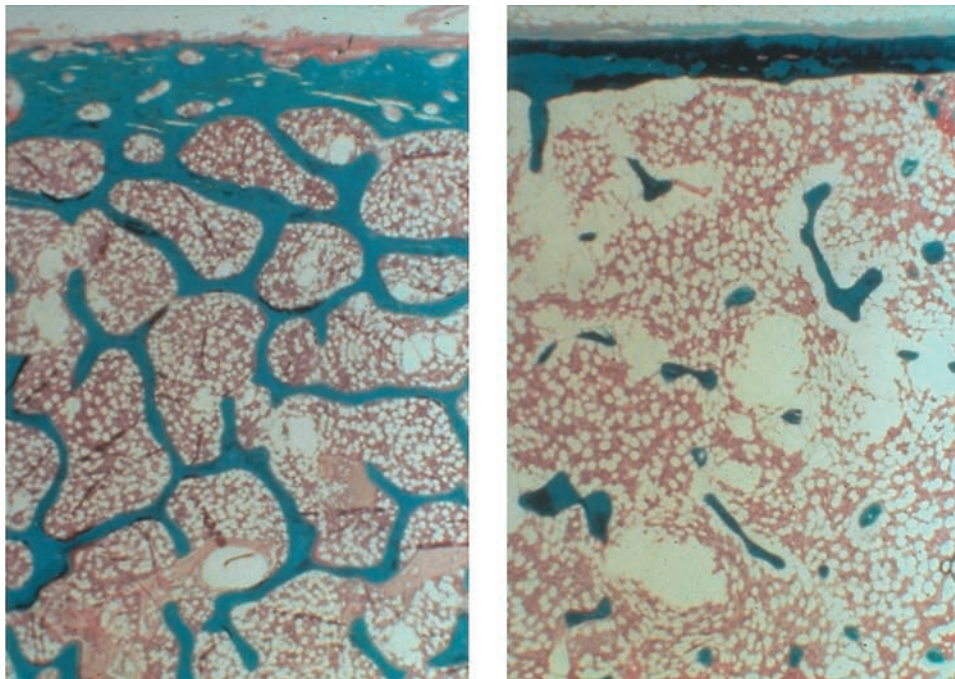


Figure 8 Bone biopsy of the anterior iliac crest in a 40-year-old female with major depression currently in remission (right) compared to the biopsy of a gender, age and BMI-matched control (left). There are two striking features. The trabeculations are markedly reduced in the depressed patient. These trabeculae are critical scaffolding for the bone and confer much of its strength. Note that the cortex is also thinner in the depressed patient. Ordinarily, glucocorticoids have much more effect on trabeculae *per se* than on the cortex. This suggests that factors other than glucocorticoids are operative in the bone loss of depression. Parenthetically, bone loss in depression is greater in the hip than in the spine. Glucocorticoid mediated bone loss occurs predominantly in the spine.

Higher depression ratings correlated negatively with the activity of left dorsolateral prefrontal cortex, while anxiety levels were positively correlated with paralimbic system activity. Successful treatment of depression was associated with inhibition of overactive paralimbic regions and normalization of hypoactive dorsolateral prefrontal cortex sites.¹²⁴ Thus, major depression seems associated with hypoactivity of cortical structures and a corresponding hyperactivity of paralimbic/subcortical loci. A recent very important finding by Drevets *et al* using *in vivo* scanning and examination of post mortem brain samples revealed a 40% decrease in the volume of the left sub-genual cortex, an area extremely important in emotion and in regulation of the HPA axis and the LC-NE system.¹²⁴ These patients were predominantly patients with melancholic depression (W Drevets, personal communication). As noted, it is of interest that the lateralization found in patients with depression is compatible with data in the rat showing that lesioning of the left infralimbic cortex causes activation of the HPA axis and of sympathetic function, while lesioning of the right produced a decrement in the activity of these systems. These data indicate that the left infralimbic region inhibits the right.¹²⁶ We therefore postulate that the left-sided defect in melancholic depressed patients leads to hyperactivity of both the amygdala and core stress system components (Figure 3, left). Conversely, in patients with atypical depression, a primary defect

in the right side may emerge, in contrast to that seen in melancholia (Figure 3, right).

Whether decrements in the volumes of the subgenual medial prefrontal cortex and hippocampus in patients with major depression are reversible or represent enduring neuropathic change is not yet clear. However, both glucocorticoids and CRH have been shown to be neurotoxic in experimental animals, so that core stress systems could participate in this neurodegeneration. In an important hypothesis by Nestler's group, and in the excellent work of Manji *et al*, abnormalities in growth factors and in other intracellular transduction mediators may play a highly significant role in the neurodegeneration in depressed patients.^{142,143} The idea is supported by the fact that antidepressants such as lithium can cause a regrowth of this lost tissue. The response of tissue trophic factors to stress and their interaction among stress mediators has not yet been elucidated.

Atypical depression

Rene Spitz made seminal observations regarding developmental abnormalities that befell infants placed in understaffed orphanages shortly after birth.^{144,145} For the first 5 or 6 months, 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. It was as if the trauma and overstimulation of their early deprivation had led to a virtual shutdown of their affective existence to protect them from unendurable pain. Subsequent studies in non-human primates who were abandoned or abused by their mothers reveal a similar behavioral withdrawal in association with hypoactivity of the HPA axis.

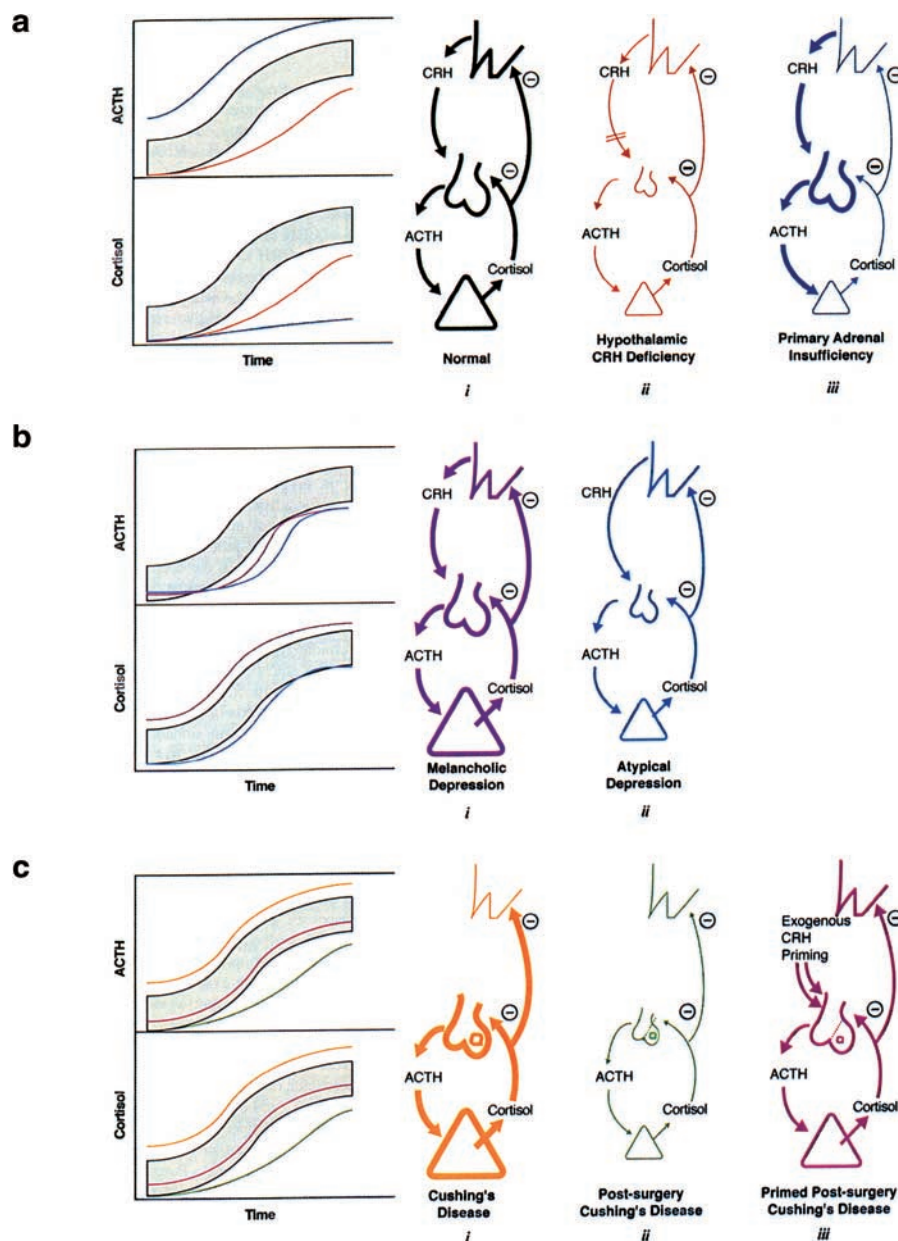
One of the implications of these findings is that the clinical presentation of melancholic depression may relate, in part, to systematic activation of stress mediators. Prompted many years ago by the idea that arousal symptoms paralleled stress system activity in melancholia, we hypothesized that the lethargy, fatigue, and hypersomnia of atypical depression was associated with a pathological reduction of stress system mediators (reviewed in ^{3,6,24}). This possibility was supported in the previously cited data in experimental animals showing that specific lesions in infralimbic cortex resulted in pathological suppression of the core stress system. The recent seminal findings of Yahuda and her colleagues showing exaggerated cortisol responses to low dose dexamethasone and other data revealing decreased urinary free cortisol excretion suggest HPA axis hypoactivity in patients with post-traumatic stress disorder.¹⁴⁶ To date, we have not found frank decreases in 24-hour urinary free cortisol in patients with atypical depression or excessive responses to dexamethasone, although a much larger series is now pending. Therefore, detecting a centrally mediated decrement in HPA axis function in patients with atypical depression was initially difficult until we developed an endocrine paradigm for the differential diagnosis between adrenal, pituitary, and hypothalamic CRH-mediated hypoactivity of the HPA axis.^{76,147} Prior efforts to document a centrally-mediated hypoactivity of the HPA axis were complicated by the facts that the HPA axis could be normally quiescent for many hours per day, and that low level pulses occurring many times a day were missing in sampling studies.

Because there were no known forms of a non-traumatically induced, centrally mediated HPA axis hypoactivity in humans, we studied patients with adrenal insufficiency as a consequence of either hypothalamic tumor or traumatic pituitary stalk section.¹⁴⁸ In the course of these studies, we identified a unique pattern of delayed plasma ACTH responses to CRH, associated with very attenuated cortisol responses to the ACTH released during CRH stimulation (Fig 9a, ii). We postulated that the blunted and delayed plasma ACTH responses reflected a lack of priming of pituitary ACTH secreting cells by endogenous CRH, similar to the blunted and delayed TSH response to TSH in patients with centrally mediated hypothyroidism. Thus, though the pituitary ACTH secreting cells are making some ACTH, they are not releasing it, so that it is kept in a secondary releasable pool and is more slowly released. In response to synthetic CRH, they eventually release some ACTH, though the response is delayed, and can

be prolonged. The blunted rather than the exaggerated cortisol responses to the blunted ACTH responses meant that their adrenals had not been hyperstimulated by excessive CRH-driven hypercortisolism, and indeed, had been hypostimulated. To support this premise, we gave these patients repeated priming pulses of human CRH prior to their next CRH stimulation test. In this context, they significantly increased their corticotroph capacity to respond to CRH challenge.¹⁴⁹ This 'hypothalamic CRH deficiency' pattern subsequently served as a template for our search of other syndromes of hypothalamic CRH deficiency. It should be noted that in contrast to hypothalamic CRH deficiency, the characteristic pattern in primary adrenal insufficiency is that of low cortisols, a very high ACTH response to CRH, and little cortisol response to these high levels of ACTH. Here, the hypothalamus and pituitary are normal, so that can respond to disinhibition mediated by an inability of the adrenals to produce adequate cortisol (Figure 9a, iii).

Like hypothalamic CRH deficiency, patients with melancholia have a blunted ACTH response to CRH. However, the response is not delayed in melancholia. A key feature of melancholia is that the cortisol response to the diminished amount of ACTH released during CRH stimulation was very robust rather than also blunted. Thus, the adrenals had become hyperresponsive to ACTH as a consequence of a hyperactive hypothalamic CRH neuron (Figure 9b, i).

We next studied patients with Cushing's disease, an illness frequently associated with depression. We had shown that in comparison to patients with melancholia who had centrally mediated hypercortisolism, the hypercortisolism of Cushing's disease is pituitary mediated¹⁵⁰ (Figure 9ci). We had also shown that more than 80% of their depressions were of the atypical pattern.¹⁵¹ We chose to study these patients after surgery when they were without the complication of the pituitary microadenoma, but left with a full complement of previously normal pituitary ACTH secreting cells. Often, these subjects are adrenally insufficient because, after the microadenoma is removed, their normal residual ACTH secreting cells are silent. This adrenal insufficiency could thus reflect long-term suppression of hypothalamic CRH or pituitary ACTH secretion in the context of many years of pre-existing hypercortisolism, much as patients on supraphysiologic doses of glucocorticoids, who must be given steroids after tapering. To study the source of the adrenal insufficiency in our Cushing's patients, we stimulated these patients with CRH. They responded with delayed and blunted plasma ACTH response and very reduced cortisol responses (the hypothalamic CRH deficiency pattern, Figure 9c, ii). We surmised that since their pituitary ACTH secreting cells could respond to exogenous CRH, they would have had levels of plasma ACTH postoperatively, if their own hypothalamic CRH cells were still secreting some CRH. These patients showed the clear 'hypothalamic' pattern in response to CRH stimulation (Figure 9c, ii). In addition, after many priming doses of synthetic human CRH, the ACTH response to CRH



was partially restored, indicating successful priming of pituitary ACTH secreting cells. To further support the premise of a decrement in hypothalamic ACTH secretion in Cushing's disease due to longstanding hypercortisolism, we found that, compared to controls, their CSF CRH levels were profoundly suppressed.⁷⁵

We were then ready to study patients with affective disorder. To determine whether patients with atypical depression show evidence of a centrally mediated hypoactivity of the HPA axis, we first studied patients with depression of seasonal affective disorder, a syndrome virtually identical to that of atypical depression.^{152,153} Patients with seasonal affective disorder responded to ovine CRH with all of the features of the 'CRH deficient' phenotype (Figure 3, right).¹⁵⁴ Blunted delayed plasma ACTH responses were associated with small rather than exaggerated cortisol

responses to CRH. Moreover, the 'CRH deficient' pattern resolved after non-pharmacologically induced remission from depression.¹⁵⁴ We have recently found that depressed children of mothers who also had histories of major depression whose parental style was hostile and overbearing showed the CRH deficiency phenotype. These individuals had participated in the NIMH Longitudinal Study of depressed mothers and their children, started over 20 years ago. Many of the children had been followed since infancy.¹⁵⁵

Almost simultaneously, we studied patients with a classic fatigue state, chronic fatigue syndrome. This illness is by no means synonymous with depression though the two disorders share some features. We also showed that these subjects had blunted ACTH and cortisol responses to CRH. They also had bimodal response in their ACTH/cortisol dose response

Figure 9 Contrasting plasma ACTH and cortisol responses to synthetic corticotropin-releasing hormone in various states. Graphs on the left show the plasma ACTH and cortisol responses to synthetic ovine corticotropin releasing hormone (CRH). The gray shaded area denotes the normal range. Diagrams on right show pathways from hypothalamus to pituitary to adrenals (triangles). Line thickness denotes relative amounts of corticotropin-releasing hormone or cortisol secreted. Negative signs denote feedback inhibition. (a) Normal (i), hypothalamic CRH deficiency (ii), and primary adrenal insufficiency (iii). Compared to controls, patients with known hypothalamic CRH deficiency have an unusual combination of a low basal plasma ACTH and cortisol levels with blunted (and delayed) plasma ACTH and cortisol responses to synthetic CRH. This pattern reflects the lack of priming of pituitary ACTH-secreting cells by endogenous CRH, and contrasts markedly with the brisk and exaggerated plasma ACTH responses seen in primary adrenal insufficiency, in which primed pituitary ACTH-secreting cells respond to synthetic CRH unrestrained by the glucocorticoid negative feedback. (b) Melancholic depression (i), and atypical depression (ii). In melancholic depression, elevated plasma cortisol levels appropriately restrain pituitary ACTH secreting cells in their response to synthetic CRH. Due to chronic centrally-mediated stimulation of the adrenals, they show an exaggerated plasma cortisol response during synthetic CRH stimulation. In chronic fatigue syndrome, seasonal affective disorder, and postpartum depression, blunted and often delayed plasma ACTH responses to synthetic CRH occur in the context of either normal or significantly reduced basal cortisol levels. Plasma cortisol responses are also significantly reduced, indicating relatively long-term hypostimulation of the adrenals by ACTH. (c) Cushing's disease: untreated (i), post-surgery (ii), and primed post-surgery (iii). The profound basal hypercortisolism of Cushing's disease is associated with exaggerated rather than restrained plasma ACTH responses (as in melancholia), indicating a gross lack of glucocorticoid negative feedback at the pituitary. Low basal cortisol levels after surgery reflect either residual suppression of remaining pituitary ACTH secreting cells or hypothalamic CRH neurons due to exposure to long-standing and profound basal hypercortisolism. This suppression lasts up to a year. Postoperative Cushing's disease patients show a blunted and delayed plasma ACTH response to synthetic CRH, suggesting that remaining pituitary ACTH secreting cells can respond to CRH when it is available. Priming with multiple pulses of synthetic human CRH largely restores the plasma ACTH response to synthetic CRH. From Gold *et al. Proc Assoc Am Phys* 1999; **111**: 22–34.

curve.¹⁵⁶ In response to low dose ACTH, patients with chronic fatigue responded with exaggerated plasma cortisol responses to ACTH. This probably reflected two factors: (1) the presence of increased sensitivity of adrenal ACTH receptors to ACTH on account of long-standing hypostimulation; and (2) the fact that even though their adrenals were small, they could produce augmented cortisol responses from an adrenal of low mass in the context of a very low dose of ACTH.¹⁵⁶ At high doses, patients with chronic fatigue syndrome had attenuated responses to ACTH. This response presumably reflects the fact that the low adrenal mass in understimulated adrenal cortices in chronic fatigue was unable to fully respond to a high dose of ACTH.

To further test the hypothesis of a centrally-mediated

HPA axis deficiency in patients with classic atypical depression, we measured plasma ACTH and cortisol levels every 3 minutes for 24 hours in four patients with atypical depression and in four controls. We reasoned that such sampling might provide sufficient resolution to detect low level pulses of ACTH and cortisol that were otherwise missed with less frequent sampling. Our data showed that patients with atypical depression had significant reductions in plasma ACTH secretion in the face of normal pituitary and adrenal components of the HPA axis, suggesting a hypothalamic CRH deficiency (Licinio and Gold, unpublished observations). Normal plasma cortisol levels may have been maintained by compensatory mechanisms. We know that in the context of unilateral adrenalectomy, the residual adrenal is stimulated by factors other than ACTH.

Only one study reports reduced CSF CRH levels in patients with major depression. This was an exceedingly carefully done study from a highly respected group that utilized an indwelling lumbar catheter for determination of CSF CRH levels over some hours. Geraciotti *et al* noted that many, but not all of the subjects of this study had atypical features.¹⁵⁷ It is noteworthy that these patients were eucortisolemic rather than hypercortisolemic. Eucortisolism in the context of a central CRH deficiency would not be surprising, given the multiple redundant mechanisms for maintaining normal glucocorticoid secretion such as enhanced sympathetic stimulation of the adrenal cortex.¹⁴⁷

Hypoactivity of one of the core stress system components that promotes arousal and diminishes food intake could contribute to the lethargy, fatigue, and hyperphagia characteristic of atypical depression.⁷ These data indicate that hypercortisolism may not be the only abnormality of HPA axis function in depressive illness. Thus, optimal functioning of the CNS requires that core stress system components remain within a carefully-maintained range, and that deficits in CNS function can occur in the context of either hyper- or hypoactive LC-NE and CRH systems.

Recent data indicate that inflammatory mediators such as IL-1 recruit hypothalamic CRH containing neurons in a negative feedback loop in which glucocorticoids exert immunosuppressive effects to prevent the immune response from overshooting.¹⁵⁸ If hypothalamic CRH neurons fail to respond adequately to cytokine stimulation, the resultant failure of adequate glucocorticoid-mediated restraint of the immune system results in a hyper-immune state. Esther Sternberg in our group found rats whose hypothalamic CRH neurons responded insufficiently to inflammatory mediators and developed a range of autoimmune diseases dependent on the trigger administered. Thus, an intact HPA axis seems necessary for an immune response of normal magnitude. In this regard, patients with chronic fatigue syndrome not only present with fatigue, but also with inflammatory symptoms such as muscle ache and joint pain and feverishness.¹⁵⁹ It is well known that many patients visit primary care facilities with complaints of fatigue and low-grade

inflammatory symptoms that have no apparent pathophysiologic basis. Many of these patients could have disinhibited immune systems on the basis of a hypoactive HPA axis.

The hyperphagia that is a defining characteristic of atypical depression is likely to lead either to obesity or a cycle of weight gain and weight loss occurring throughout recurrent episodes of depression. Because weight that is regained after weight loss may be preferentially distributed as intra-abdominal fat, either sustained obesity or weight cycling could result in adverse

metabolic consequences conducive to coronary artery disease. As noted, the visceral fat mass is metabolically very active and can lead to several problems such as premature cardiac disease. On the other hand, our data in patients with the atypical depression of seasonal affective disorder suggest that bone mineral density is not reduced (Gold *et al*, unpublished observations), in contrast to the group of depressed patients in whom mean 24-hour urinary free cortisol excretion was elevated.

For a systematic comparison of the potential long-

Table 1 Postulated clinical differences and differential long-term medical consequences of melancholic and atypical depression

	Melancholic	Atypical
Clinical Phenotype		
Level of arousal	Hyperaroused	Hypoaroused, apathetic
Anxiety level	Anxious	Generally not anxious
Reactivity	Relatively unreactive to environment	Reactive to environment
Affect	Stereotyped affect	Stereotyped affect, intermittent reactivity
Emotional memory	Predominance of painful emotional memory	Relatively out of touch with past
Capacity for pleasure	Anhedonic	Anhedonic
Cognition	Decreased concentration, perseveration	Loss of focus
Behavior	Shift to relatively well-rehearsed behaviors	Unmotivated, inactive
Neurovegetative		
Sleep	Decreased sleep; poor quality	Increased sleep; poor quality
Appetite	Decreased food intake, weight loss	Increased food intake, weight gain
Energy level	Overt energy level variable	Marked lethargy and fatigue
Libido	Diminished	Diminished
Neuroendocrine		
HPA axis	Centrally-activated	Centrally-mediated hypoactivity
GH axis	Suppressed	Suppressed
Reproductive axis	Suppressed	Suppressed
Autonomic		
Sympathetic activity	Increased	Decreased
Body Composition		
Body Mass Index (BMI)	Normal	High
Lean body mass	Decreased (sarcopenia)	Normal
Total body fat	Normal or increased	Increased
Visceral fat	Increased	Increased
Metabolic		
Insulin sensitivity	Decreased	Decreased
Lipid metabolism	Dyslipidemia	Dyslipidemia
Coagulation	Hypercoagulable/decreased fibrinolysis	Hypercoagulable/decreased fibrinolysis
Immune Function	Relatively immunosuppressed	Relatively immunoenhanced
Medical Sequelae		
Heart disease	Premature ischemic heart disease	Premature ischemic heart disease
Osteoporosis	Premature osteoporosis	Normal bone
Infection/inflammation	Increased susceptibility to infection	Increased susceptibility to inflammation
Neurodegeneration	Hippocampus/medial prefrontal cortex	?

Melancholic depressed patients, in many instances, should have different medical complications than patients with atypical depression. We suggest that the common medical complications we predict might be the same, occur because of different mechanisms. For instance, we predict that melancholic patients will have decreased insulin sensitivity because of hypercortisolism and increased NE secretion, while atypical patients will be insulin-resistant because of low growth hormone secretion and a non-cortisol mediated increase in visceral fat.

term medical complications of melancholic and atypical depression, please see Table 1.

Summary and conclusions

In summary, the available data suggest that there is concomitant activation of the CRH and LC-NE systems in melancholic depression, and that CRH, NE, and cortisol participate in mutually reinforcing positive feedback loops that can generate a tremendous and prolonged response involving many brain areas. Both CRH and NE activation may potentiate the intensity of future stress responses by enhancing the encoding of adverse emotional memory and by sensitizing specific substrates so that subsequent responses are enhanced. Because CRH and the glucocorticoids are neurotoxic, a progressive loss of critical tissue may theoretically occur. It is of interest that as early as 1984, investigators postulated a role for CRH that included not only transducing symptoms of melancholic depression but also in sensitizing the stress system (Figure 10). We are now, of course, armed with the revolution in molecular genetics, have gotten inside the cell, and have many new mediators to understand, including CRHR-1 and CRHR-2, their endogenous ligands, and the CRH binding protein.

The neurobiology of major depression with melancholic features suggests a syndrome reflecting a dysregulation of an essential adaptive response system called into play frequently in all of us, rather than exotic pathophysiological changes that are otherwise rarely seen. The dysregulation of stress system function that involves genetic, constitutional, and environmental factors allows the interposition of multiple reinforcing feedback loops that are likely to contribute to the clinical and biochemical manifestations of major depression.

The association of a syndrome characterized by leth-

argy, fatigue, apathy, hyperphagia, and hypersomnia, with a pathologic downregulation of a critical stress-responsive arousal-producing component of the stress system, is of both practical and theoretical significance. This finding provides new targets for diagnosis and therapeutic intervention. In addition, the definitive differentiation of depressive syndromes into distinct biochemical phenotypes has implications for molecular genetic studies and the search for additional long-term medical consequences. In particular, failure to effectively differentiate biochemically distinct subgroups of patients with melancholic and atypical major depression, on the basis of factors that differentially influence susceptibility to medical illness, could complicate the systematic identification of individuals with depressive illness at risk for cardiovascular disease, osteoporosis, and inflammatory disease. In addition, failure to stratify depression on these, and hopefully more precisely identified abnormalities in the future, could impede scientific inquiry.

The enhanced susceptibility of patients with major depression to the premature onset of complex diseases that are frequently seen as we age suggests that the pathophysiological changes of major depression, especially with melancholic features, leads to a form of premature aging. Melancholic patients have the premature onset of complex disorders such as coronary artery disease and osteoporosis and are likely to die sooner. Other stigmata of aging such as the more frequent awakenings during sleep in the elderly are also present in melancholic depression. We postulate that patients with melancholic depressive episodes also have premature progressive decrements in growth hormone and DHEA secretion.

In a recent screen for gene mutations that extend life in drosophila, the mutant line methuselah displayed an approximately 35% increase in average life span and enhanced resistance to various forms of stress including starvation, high temperature, and free radical generation.¹⁶⁰ Preliminary analysis of the methuselah gene predicted a protein with homology to the well-known family of seven transmembrane receptors involved in neurotransmission, endocrine regulation, and metabolism. In *C. elegans*, life span and stress are also closely associated, and organisms selected for postponed senescence also show increased tolerance to heat, starvation, and oxidative damage.¹⁶¹ Thus, there is likely to be a price for each activation of the stress response, and a higher price for patients with an illness that involves its long-term activation.

Emotional responses call upon disparate sites in brain for the integration of previously encoded memories and their significance, assessment of the present reality, and initiation of a relatively well-rehearsed plan of action and reflexive physiological and metabolic changes. Much of the brain is called into play to accomplish these tasks.¹⁶² Similarly, the pronounced changes in neuroendocrine function and autonomic outflow associated with depression potentially influence an enormous number of somatic cells and neurons. Consequently, previous concepts of depression as

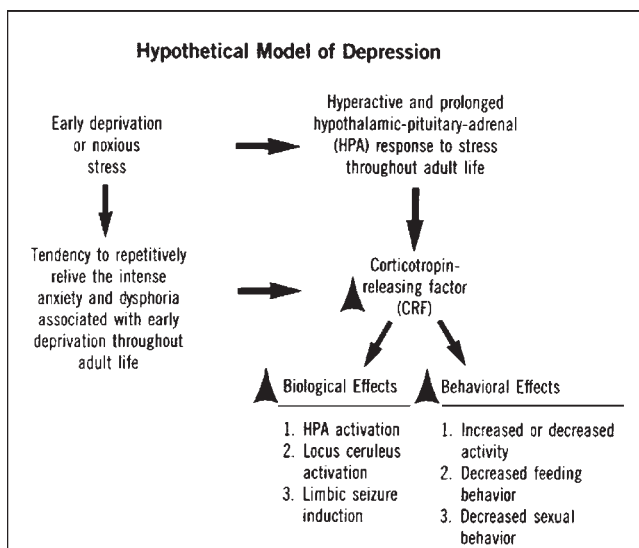


Figure 10 Early formulation of relation between CRH and depression. From Gold *et al. Am J Psychiat* 1984; **311**: 1127.

a specific disorder affecting mood have now given way to an appreciation of this disorder as a systemic illness that exerts enormous effects on the CNS and periphery.

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