Overview

MORE THAN ONE-HALF OF A DECADE OF EXPERIENCE WITH VENLAFAXINE DUAL SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR

Charles B. Nemeroff, M.D., Ph.D.*

There are many telling reasons to assemble a special issue of *Depression and Anxiety* at this time on venlafaxine, the dual serotonin-norepinephrine reuptake inhibitor, that is currently approved in the United States for the treatment of major depression and generalized anxiety disorder.

First, there has been increasing evidence largely compiled by Bech and his colleagues in Denmark that antidepressants that inhibit both norepinephrine and serotonin reuptake (SNRI) are more effective in severe and refractory depression than those that inhibit uptake of a single monoamine neurotransmitter. In addition, patients with major depression treated with dual reuptake inhibitors may achieve remission more frequently than those treated with single monoamine reuptake inhibitors. This is not a trivial point in view of the considerable morbidity associated with chronic depression. There is now convincing data not only of the potential suicide risk in partially treated depressed patients, but the emerging data base that suggests that depression is associated with a significantly increased risk for both the development of, and poor outcome after, both myocardial infarction and stroke.

The present volume reviews in a comprehensive fashion the neurobiology of depression with a focus on the pathophysiologic involvement of serotonergic and noradrenergic systems, as well as the preclinical and clinical neuropharmacology of venlafaxine. Much emphasis is paid to summarize in a succinct manner the pharmacokinetics and drug–drug interaction profile of this agent, as well as its efficacy in the treatment of depression, severe depression, refractory depression, as well as geriatric depression. Moreover, particular consideration is given to the growing awareness of the remarkably high comorbidity of mood and anxiety disorders, and the efficacy of venlafaxine in these states. The use of venlafaxine in generalized anxiety disorder as well as in other psychiatric conditions is adequately reviewed, as is the use of this dual reuptake inhibitor in children and adolescents. Finally, the importance of measures of quality of life in assessing treatment response in mood and anxiety disorders is described, as well as pharmacoeconomic studies which seek to determine the cost utility of antidepressant treatment in this common and devastating set of conditions.

There is little doubt that the introduction of venlafaxine has had a remarkable impact on clinical practice. I have had more than 25 patients who have failed multiple trials with virtually all of the antidepressants available who have responded to venlafaxine often with complete remission. One such case which may be worth recounting is that of the CEO of a major Atlanta company who had been admitted to the inpatient service with the diagnosis of early Alzheimer's disease and comorbid depression. He had a mini-mental state exam score of 20 and a past history of several severe depressions that had responded to either tricyclic antidepressant or electroconvulsive therapy. He failed treatment with two of the more modern antidepressants, and after eleven ECT treatments was considerably more confused and, of great concern, had no response whatsoever in terms of depression severity. Treatment was initiated with venlafaxine and after treatment with this agent for eight weeks at a dose of 375 mg per day, he not only achieved a complete remission of his depression, but his "dementia" completely resolved, with a mini-mental state score of 29 upon discharge. He, in fact, does not have Alzheimer's disease, but instead had a classic case of pseudodementia.

Discussing this case with my colleagues, it is clear that this is not an unusual outcome. It is my hope that this volume will communicate to clinicians in both academia and in the community the enthusiasm that the authors have for this dual reuptake inhibitor. Indeed, venlafaxine offers an important treatment option for both the psychiatrist and primary care physician for achieving a state of "wellness" in a broad spectrum of patients.

With the advent of new functional brain imaging techniques, particularly positron emission tomography, future developments in the field will likely allow for determination of which particular neurotransmitter system abnormality exists in a given patient, and the rational prescribing of antidepressants to target such abnormalities. This would finally allow for long awaited biological predictors of antidepressant drug responsiveness.

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

*Correspondence to: Charles B. Nemeroff, M.D., Ph.D., Dept. of Psychiatry, and Behavioral Sciences, Emory University School of Medicine, 1639 Pierce Drive, Atlanta, GA 30322-4990.

Received for publication 6 October 2000; Accepted 6 October 2000

DEPRESSION AND ANXIETY, VOLUME 12, SUPPLEMENT 1:2–19 (2000)

Research Reviews

ROLE OF SEROTONERGIC AND NORADRENERGIC SYSTEMS IN THE PATHOPHYSIOLOGY OF DEPRESSION AND ANXIETY DISORDERS

Kerry J. Ressler and Charles B. Nemeroff, M.D.*

There is abundant evidence for abnormalities of the norepinephrine (NE) and serotonin (5HT) neurotransmitter systems in depression and anxiety disorders. The majority of evidence supports underactivation of serotonergic function and complex dysregulation of noradrenergic function, most consistent with overactivation of this system. Treatment for these disorders requires perturbation of these systems. Reproducible increases in serotonergic function and decreases in noradrenergic function accompany treatment with antidepressants, and these alterations may be necessary for antidepressant efficacy. Dysregulation of these systems clearly mediates many symptoms of depression and anxiety. The underlying causes of these disorders, however, are less likely to be found within the NE and 5HT systems, per se. Rather their dysfunction is likely due to their role in modulating, and being modulated by, other neurobiologic systems that together mediate the symptoms of affective illness. Clarification of noradrenergic and serotonergic modulation of various brain regions may yield a greater understanding of specific symptomatology, as well as the underlying circuitry involved in euthymic and abnormal mood and anxiety states. Disrupted cortical regulation may mediate impaired concentration and memory, together with uncontrollable worry. Hypothalamic abnormalities likely contribute to altered appetite, libido, and autonomic symptoms. Thalamic and brainstem dysregulation contributes to altered sleep and arousal states. Finally, abnormal modulation of cortical-hippocampal-amygdala pathways may contribute to chronically hypersensitive stress and fear responses, possibly mediating features of anxiety, anhedonia, aggression, and affective dyscontrol. The continued appreciation of the neural circuitry mediating affective states and their modulation by neurotransmitter systems should further the understanding of the pathophysiology of affective and anxiety disorders. Depression and Anxiety, Volume 12, Supplement 1:2–19, 2000. *© 2000 Wiley-Liss, Inc.*

Key words: *serotonin; norepinephrine; depression; anxiety; pathophysiology*

INTRODUCTION

Mood and anxiety disorders are generally classified as separate types of syndromes, e.g., see DSMIV and ICD10. It is now clear, however, that depression and anxiety share many overlapping symptoms including fatigue, impaired concentration, irritability, sleep disturbance, and somatization in addition to subjective experiences of nervousness, worry, and restlessness [Ninan, 1999]. They may also share a common pathophysiology [Weiss et al., 1994]. In fact, the key difference between depression and generalized anxiety disorder is whether the patient subjectively has a primarily depressed or anxious mood, with many other symptoms being shared. The National Comorbidity Survey reported that 58% of patients with major depression also fulfilled criteria for an anxiety disorder

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

*Correspondence to: Dept. of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1639 Pierce Dr., Atlanta, GA 30322.

[Kessler et al., 1996]. Furthermore, most patients with primary anxiety disorders also experience major depressive episodes. The finding that 68% of individuals with co-morbid depression and anxiety were anxious for over 10 years before the eventual development of depression suggests overlapping mechanisms. The co-occurrence of anxiety and affective syndromes, anxiety symptoms in patients with syndromal mood disorders, depressive symptoms in patients with syndromal anxiety disorders, subsyndromal affective and anxiety symptoms, and so-called mixed depression and anxiety have received considerable attention [Gulley and Nemeroff, 1993].

Discussion of different neural systems underlying the pathophysiology of depression and anxiety has similarly been separated. There is abundant data suggesting neurobiologic mechanisms including norepinephrine (NE) serotonin (5HT) dysregulation, corticotropin-releasing factor (CRF) stress response abnormalities, and newer data showing abnormalities of neurotrophic factors and cellular transduction factors that are pathologically involved in these disorders. In parallel, there have been great strides in the preclinical understanding of limbic regulation mediating stress and fear responses [Davis, 1998a; LeDoux, 1998], and human neuroimaging studies implicating certain structures in depression and anxiety disorders [Drevets, 1998]. Furthermore, infant reactivity and behavioral inhibition as early markers of affective responsiveness predict greater vulnerability to affective and anxiety disorders in adulthood [Kagan and Snidman, 1999].

The crucial roles of NE and 5HT circuits in these disorders were largely first uncovered by an understanding of empirically discovered antidepressants [Schildkraut, 1965; Maes and Meltzer, 1995] together with evidence that antihypertensives such as reserpine that depleted monoamines sometimes led to depression [Freis, 1954]. Despite much progress in our understanding of neurobiology and physiology of affective illnesses, perturbation of NE and 5HT with antidepressants remain our primary means of treating these debilitating diseases. The primary pathophysiological alterations in these disorders, however, are increasingly less likely to be solely or even primarily the NE and 5HT systems. Rather their involvement is more likely due to their role in modulating, and being modulated by, other neurobiologic systems that together mediate the symptoms of affective illness. Abnormalities in NE and 5HT likely contribute significantly to symptomatology, however, and actions on these circuits seems to be critical in treatment response.

In this monograph, we focus on the neurobiology of the NE and 5HT systems in the context of other neural systems with demonstrated abnormalities in depression. Space constraints preclude an entirely comprehensive treatise, therefore we attempt to focus on those dysregulated systems that are most accepted and that illustrate the critical role of NE and 5HT in modulating functional neural circuits. We present a model based on the extant literature that we hope will stimulate continued exploration of how currently available antidepressants exert effects on the broader neural systems involved in the pathophysiology of depression and anxiety disorders.

NEUROBIOLOGY OF NOREPINEPHRINE AND SEROTONIN SYSTEMS

NEUROANATOMY OF NE AND 5HT SYSTEMS

Both the NE and 5HT systems project from the brainstem extensively throughout cortical and subcortical structures [Levitt et al., 1984]. Cell bodies containing NE are found within the relatively discrete locus coeruleus (LC) and within the lateral tegmental nuclei that are more loosely scattered throughout the ventral pons and medulla. The LC comprises over 70% of the forebrain NE innervation, projecting to the cortex, subcortical, and limbic structures in addition to cerebellum, medulla and spinal cord. Each LC neuron has a wide, but limited projection. Such projections seem to be organized along a dorsal to ventral gradient within the LC [Lindvall and Bjorklund, 1984]. The LC cortical projections are to layers I, IV, and V, suggesting a significant role of NE in modulating intracortical and thalamocortical activity [Levitt et al., 1984]. The lateral tegmental NE cell groups project primarily to hypothalamus, lower brainstem, and spinal cord. Most NE neurons use conventional synapses, though there is some evidence that NE may also be released in a limited amount into non-synaptic extracellular space, thus serving a limited paracrine role [Papadopoulos et al., 1990].

The principal neural inputs that modulate LC activity and subsequent NE release are two brainstem nuclei, the nucleus paragigantocellularis (PGi) and the nucleus prepositus hypoglossi (PrH). The PGi has excitatory CRF and glutamatergic inputs and likely plays a key role in the interaction between stress response and NE activity leading to arousal [Valentino et al., 1993]. The PrH provides the primary inhibitory control over LC with GABA-ergic and enkephalinergic inhibitory inputs. PrH participates in oculomotor function and may assist in modulating attentional changes accompanying visual shifts. Other brainstem nuclei [raphe nuclei and ventral tegmental area (VTA)], hypothalamus, periaqueductal gray, and paraventricular nucleus, along with limited cortical and subcortical input provide precise regulation of LC firing, likely allowing its complex and variable firing related to behaviorally significant tasks. There is also evidence for a direct amygdala projection to LC utilizing CRF, contributing to excitation during the stress/fear response [Van Bockstaele et al., 1999]. It is also important to note that the LC, like

other CNS structures, may be influenced by the products of peripheral endocrine glands such as glucocorticoids [Owens et al., 1990].

Serotonergic neurons are primarily located within two brainstem structures, the dorsal and median raphe nuclei. Neurons within these nuclei have different, but overlapping projection patterns along with different axonal morphology. For example, limbic structures (e.g., hippocampus and septum) seem to be primarily innervated by median raphe neurons, whereas basal ganglia structures (e.g., striatum and substantia nigra) are primarily innervated by those in the dorsal raphe [Frazer and Hensler, 1994]. Many areas have broadly overlapping projections, however, and single neurons can innervate several synaptically interconnected regions [Azmitia, 1999; Tork, 1990]. Serotonergic axons exhibit different morphology based on their origin. Median raphe neurons typically have large spherical varicosities with extensive repeated synapses, whereas dorsal raphe axons have small fusiform boutons, diffusely branching fibers with fewer classic synapses and possibly more non-synaptic release of transmitter. Serotonergic synapses are most densely concentrated in limbic regions including the amygdala and bed nucleus of the stria terminalis (BNST), thought to play a seminal role in anxiety [Davis, 1998b], as well as the ventral striatum and hypothalamus. There are much less dense but not insignificant concentrations in cortical regions as measured by serotonin transporter binding in humans and non-human primates [Gurevich and Joyce, 1996; Smith et al., 1999].

Principal inputs regulating raphe neuron firing include afferent projections from brainstem nuclei such as the substantia nigra, VTA, and LC and nucleus tractus solitarius (NST), with lesser hypothalamic, thalamic, and limbic inputs [Frazer and Hensler, 1994; Tork, 1990]. Some cortical projections also have significant effects on serotonergic activity [McDonald, 1998], with evidence that ventral or orbital prefrontal cortex (PFC) has a direct inhibitory effect on raphe activity [Hajos et al., 1998]. This pathway is of interest because these PFC areas may be hyperactive in some anxiety and depressive states [Drevets, 1998]. Like the LC, raphe neuronal activity may also be modified by circulating hormones, e.g., glucocorticoids or gonadal steroids.

NEUROTRANSMITTER RECEPTORS MEDIATING NE AND 5HT ACTION IN THE BRAIN

Within the last decade, knowledge concerning the number and complexity of NE and 5HT receptors has exponentially increased. There are several excellent reviews on these receptors [Weiner and Molinoff, 1994; Aghajanian, 1995; Glennon and Dukat, 1995; Buhot, 1997; Hoyer and Martin, 1997; Mansour et al., 1998], and they are therefore only discussed briefly here. The receptors were initially identified and characterized by electrophysiologic studies. With the recent advances in molecular biology, they are now being critically dissected in terms of cellular localization, anatomic localization, effector mechanism (channel vs. second messenger), and transcriptional, translational, and post-translational regulation. The multiple known receptors for each neurotransmitter are briefly described below.

Each neurotransmitter system is comprised of pre- and postsynaptic, excitatory and inhibitory receptor types. There seem to be fewer NE than 5HT receptor types. The NE receptors [reviewed in Weiner and Molinoff, 1994] consist of three families: β-adrenergic receptor (βAR), α_1 adrenergic, and α_2 adrenergic receptors. βAR is the principle postsynaptic receptor and is excitatory on the postsynaptic membrane. At least three different subtypes of βAR exist (βAR_{1-3}), and all mediate transmission through activation of adenylate cyclase. The α_1 receptors are excitatory and are located postsynaptically. There are at least two subtypes, each of which may activate the protein kinase C (PKC) pathway. The α_{1A} is linked to Calcium channel opening and α_{1B} is linked to phospholipase C and IP3 activation. The α_2 class of receptors are all inhibitory and may be located both pre- and postsynaptically. There are at least three subtypes of α_2 receptors, all of which mediate their effect by inhibiting adenylate cyclase activity.

The 5HT receptors are greater in number and seem to be more heterogeneous [reviewed in Aghajanian, 1995; Mansour et al., 1998]. At least 14 subtypes have been cloned and identified. The $5HT_1$ class are located both pre- and postsynaptically, and is inhibitory through reduction of adenylate cyclase activity via G_i activation. The $5HT_2$ class is predominantly postsynaptic, and excitatory through activation of phospholipase C via G_o. The $5HT_4$, $5HT_5$, and $5HT_6$ classes all activate adenylate cyclase via G_s. In contrast, the $5HT_3$ receptor exerts its excitatory effects by acting as an ion channel.

INTERACTION BETWEEN NE AND 5HT SYSTEMS

There is significant interconnectivity between the locus coeruleus (LC) and raphe nuclei (RN), and their actions tend to be mutually inhibitory [reviewed in Mongeau et al., 1997; see Fig. 1). Via the $5HT_2$ receptor, the dorsal raphe nucleus (DRN) activates the PrH nucleus, that is the primary inhibitory input to the LC. DRN also inhibits PGI activation of LC via $5HT_{1A}$ receptors. In return, the LC exerts inhibitory action on the median raphe nucleus (MRN) via α_2 receptors. The LC seems to have both excitatory and inhibitory actions on DRN via α_1 and α_2 receptors, respectively. In addition to control of neuronal firing, another level of modulation seems to occur by presynaptic control of 5HT and NE release via so-called heteroceptors. Thus inhibitory α_2 receptors have been localized on 5HT terminals and excitatory $5HT_3$ re-

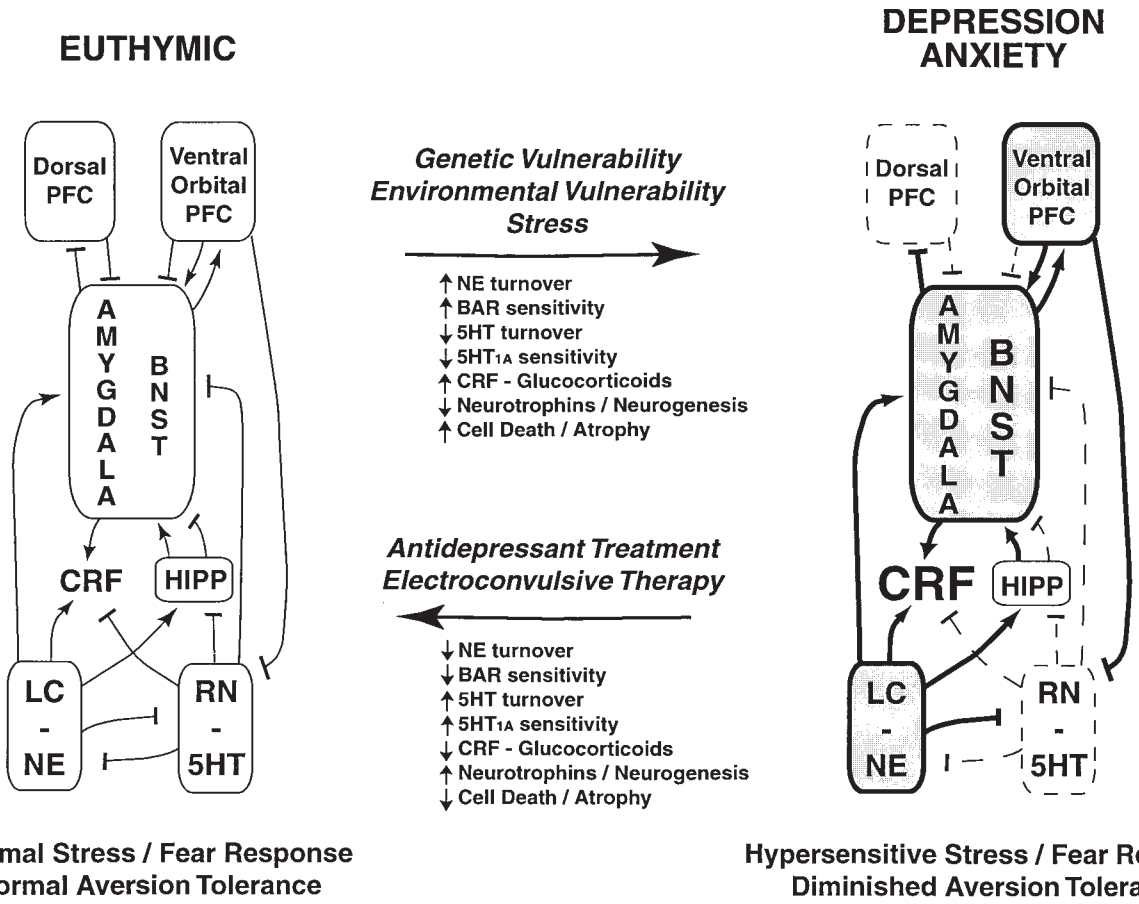

Figure 1. The brainstem modulatory nuclei, locus coeruleus with norepinephrine (LC-NE) and raphe nuclei with serotonin (RN-5HT), are shown with their primary excitatory (→) and inhibitory (—|) effects on limbic circuitry. The limbic system modulates affective state and approach/avoidance behavior, states that can be modeled by stress/fear response and aversion tolerance. During the euthymic state, stress or activating stimuli lead to an initial activation of the LC-NE system via release of corticotropin releasing factor (CRF) from the amygdala and from the paraventricular nucleus of the hypothalamus. This release is opposed by the inhibition of these circuits via 5HT release that promotes tolerance to aversion and decreases the amygdala/bed nucleus of the stria terminalis (BNST) stress response. Other limbic regions, including hippocampus (HIPP) are modulated by these pathways, with NE tending to increase memories of aversive context and 5HT tending to decrease such memories. Both dorsal prefrontal cortex (PFC) and ventral/orbital PFC are thought to be critical in mediating extinction of fearful memories and aversion tolerance. The ventral prefrontal areas, however, may also activate the affective circuitry and may inhibit RN activity (see text). NE and 5HT have complex modulatory roles in cortical functioning are not easily summarized in this diagram. Multiple genetic and environmental determinants lead to alterations in these systems that lead to a dysregulated state of functioning in depression and anxiety disorders (shown above: thick lines and hash lines represent significantly increased and decreased activity, respectively). In this state, the LC-NE system is hyperresponsive to stress/fear stimuli and aversion responsiveness, and the RN-5HT system is hyporesponsive with decreased inhibition of stress reactivity and decreased tolerance to aversion. The cortical modulation of limbic reactivity is dysregulated and likely contributes to the altered NE/5HT functioning. Additionally, dysregulation of the NE/5HT systems contributes to abnormal sleep, attention, concentration, appetite, and libido via pathways that are not apparent in this diagram. Antidepressant or electroconvulsive treatment is associated with decreased NE turnover and receptor sensitivity, and increased 5HT turnover and receptor sensitivity. These alterations are coupled with alterations in the CRF/glucocorticoid system and changes in neurotrophic factors and cell growth that are thought to be associated with recovery from depressed and anxiety states.

ceptors have been localized on NE terminals. This mechanism has been proposed to lead to negative feedback onto the 5HT neurons, in which increasing extracellular 5HT concentrations lead to increased local NE release mediated by the $5HT_3$ receptor, that may subsequently decrease or tonically inhibit 5HT release via NE activation of the presynaptic α_2 receptor [Mongeau et al., 1997].

PHYSIOLOGICAL ROLES FOR THE LC-NE SYSTEMS

Several lines of evidence suggest that NE has a preeminent role in organizing the behavioral state of mammalian organisms. This is most pronounced in regards to vigilance, arousal, activation of the stress response, and modulation of memory systems with regard to salient, particularly aversive, stimuli. Recordings from awake, behaving rodents have consistently shown that the LC fires fastest when alert and awake, slower during quiet wakefulness, more slowly during slow wave sleep, and is silent during rapid eye movement sleep [Foote and Aston-Jones, 1995]. In the awake animal, there is rapid variability in firing rate, with highest firing rates consistently seen with behaviorally orienting responses. Firing is phasically most intense when an automatic behavior (i.e., grooming) is suddenly disrupted, causing rapid orientating responses [Aston-Jones et al., 1991a]. Primate studies have also shown a complex response, such that repeated new stimuli lead to rapid desensitization with decreased phasic responses. New faces and other complex, meaningful stimuli consistently elicit strong, phasic LC firing. Besides novelty, stress seems to be a robust activator of LC firing [Valentino and Aston-Jones, 1995]. Numerous modalities of stress from hypoglycemia, hyperthermia, hypotension, restraint, footshock, and aversive auditory stimuli increase LC discharge [Aston-Jones et al., 1991b; Valentino et al., 1993]. These various stressors are thought to activate LC firing via PGi and amygdala afferents [Van Bockstaele et al., 1999]. Consistent with this, it has been proposed that activation of the central CRF system, as has been repeatedly shown in depression [Nemeroff, 1996; Plotsky, 1998; Arborelius, 1999], would lead to persistent activation of the LC with disrupted responses to brief sensory stimuli [Valentino and Aston-Jones, 1995].

The role of NE release in cortical and subcortical structures has been studied in brain slices and in vivo in target areas. The consistent findings are that NE application or LC stimulation seem to "gate" inputs to target neurons with an increase of subthreshold inputs to threshold levels, eliciting firing of the synaptic targets [Waterhouse et al., 1988]. In the thalamus, NE seems to enhance the responsiveness of thalamic neurons to inputs, switching their primary drive from tonic rhythmic bursting to modulating sensory and motor throughput. This is the likely mechanism by which LC activity is correlated with the change in thalamocortical inputs from slow wave bursting when drowsy to complex firing when alert [Aston-Jones et al., 1991b]. This is also seen in the EEG correlate of arousal that has been shown to be LC-NE dependent during some forms of stress [Valentino et al., 1993].

Potentiation of target neuron firing has been found in broad areas from the visual system where NE enhances the precision and amplitude of responsiveness [Kasamatsu et al., 1984] to the hippocampus where NE increases signal-to-noise ratio of transmission [Mongeau et al., 1997]. NE application or LC firing has been shown to facilitate long-term potentiation (LTP) in several regions [Hopkins and Johnston, 1988]. Furthermore it has been hypothesized that NE is critical to regulation of hippocampal function [Curet and deMontigny, 1988.] NE elevation switches hippocampal function from a lowered state of memory formation when not behaviorally activated to a state of enhanced stimulus detection and encoding when aroused with novelty or stressed with aversion [Gray, 1987]. It has been proposed that NE overactivity might result in excess hippocampal functioning in the stressed/aroused state, with enhanced or oversensitive memory to aversive stimuli [Mongeau et al., 1997]. The amygdala also contains extensive NE efferents, and many NE projections also arise from the NST, that is activated by vagus nerve autonomic activation. NE in the amygdala has been shown to be critical for the HPA stress response [Feldman and Weidenfeld, 1998], and potentiates formation of aversive memories [Valentino et al., 1993; Davis, 1998a]. As schematized in Figure 1, NE modulation of amygdala function is thought to regulate stress or fear related memory storage in other brain regions [Cahill and McGaugh, 1998], including the hippocampus, nucleus accumbens, and BNST, that is thought to be involved in anxiety regulation [Davis, 1998b].

The role of the LC-NE system is crucial in organizing the behavioral state of the organism. Cortical LC projections suggest a role in mediating attention and concentration. Thalamic projections suggest roles in coordinating overall activity related to levels of arousal and sleep, along with a role in sensory-motor gating. Hippocampal and amygdala projections modulate learning, particularly of memories associated with stress or aversive experience. Hypothalamic NE projections may exert neuroendocrine effects related to arousal and stress response. The complex firing dynamics of the LC-NE system mediate arousal state throughout the CNS and likely provide important modulatory inputs on synaptic transmission at behaviorally significant times. The system likely mediates proper timing of learning, memory, arousal, and concentration in accordance with salient aspects of the organism's environment. Clearly, functional alterations are likely to mediate some symptoms of depression including interference with normal concentration, memory, attention, arousal, and sleep.

PHYSIOLOGICAL ROLES FOR THE RAPHE-5HT SYSTEM

The role of 5HT in brain and behavioral physiology is somewhat more obscure than NE. In addition to more receptor diversity, the electrophysiological data is less clear in its implications. 5HT seems to have roles in sleep, appetite, memory/cognitive function, impulsivity, sexual behavior, and motor function along with

modulation of limbic/affective responsiveness. In addition to these more classic modulatory roles in behavior, 5HT is involved in neuronal homeostasis and as a trophic factor in neuronal growth and differentiation.

Firing of the raphe nuclei (RN) with associated 5HT release parallel the activity of the LC-NE system. During REM sleep they are silent, with approximately 3 Hz tonic firing with quiet wakefulness, and 6 Hz tonic firing in more aroused states. There is some controversy regarding the level of firing related to stress, with different paradigms finding significant increases in some models [Chaulouff et al., 1999], whereas others find no increase in raphe activity with salient behavioral stressors [Jacobs and Fornal, 1999]. It is clear, however, that the primary activity that leads to increased RN firing is rhythmic, often head or neck focused activities such as chewing, licking or grooming, in addition to truncal rhythmic behavior such as walking or running [Jacobs and Fornal, 1995; Azmitia, 1999]. These authors argue that the findings of increased serotonin release in stress are likely related to such motoric activity. Most of the activities cited as particularly salient for RN firing can also be viewed as internally directed behavior, as opposed to LC firing that seems to be most sensitive to activation of externally directed attention. In direct contrast to the NE system, there is significant decrease in RN firing rate with attentional shifts to orienting responses. The repetitive behaviors and thoughts characteristic of certain anxiety disorders such as OCD may be a means of activating their brain 5HT system for some beneficial effect on the neural system [Jacobs and Fornal, 1999].

Serotonin has many electrophysiologic functions in its target areas [Aghajanian, 1995], and the combination of excitatory, inhibitory, and modulatory roles lead to a more complex electrophysiology than that of NE that can be summed up as potentiating gating. The role of 5HT in sleep is largely mediated via action on the cholinergic nuclei of the brainstem. Decrease in $5HT_{1A}$ activation is thought to be responsible for the emergence of PGO spikes and REM sleep. Cortical modulation by 5HT is mediated by multiple excitatory and inhibitory receptors. As with LC-NE activity, there seems to be a complicated dose-response relationship in cortical circuitry modulated by 5HT. It seems that in some cases, moderate levels of 5HT are needed to potentiate glutamatergic action, but higher 5HT levels lead to inhibition [Ashby et al., 1990; Aghajanian, 1995]. Although its role in cortical processing is complex [Buhot, 1997], its importance is clearly implicated by the serotonergic modulation by hallucinogens (e.g., LSD and mescaline) and atypical antipsychotics (e.g., clozapine, quetiapine) [Aghajanian and Marek, 1999]. Hypothalamic modulation by 5HT may be involved in appetite control, modulation of the HPA stress response, and sexual behavior [Frazer and Hensler, 1994; Olivier et al., 1998; Rainnie, 1999].

The limbic system contains dense serotonergic projections. In the CA1 region of the hippocampus, 5HT produces membrane hyperpolarization and decreases LTP production [Mongeau et al., 1997]. It seems to inhibit a population of feed-forward interneurons on the CA1 pyramidal cells, thus attenuating inhibitory postsynaptic potentials [Segal, 1990]. It has been proposed that its role in the septo-hippocampal system is to trigger behavioral inhibition (i.e., freezing instead of flight or aggression) when in the alert or stress mode of hippocampal functioning [Gray, 1987]. Multiple lines of evidence regarding 5HT functioning in limbic circuitry have led some to argue that 5HT increases the hippocampal 'resilience system', increasing the tolerance toward aversive experience [Mongeau et al., 1997; schematized in Fig. 1). Serotonin densely innervates the amygdala [Tork, 1990; Azmitia, 1999] and is also involved in regulation of the HPA axis at this level [Feldman and Weidenfeld, 1998]. Furthermore, several lines of evidence suggest that 5HT decreases amygdala activity and may decrease learning of aversive stimuli. Studies of fear conditioning have shown that 5HT inhibits cortical and thalamic excitatory drive into lateral nucleus of the amygdala, that is critical in fear conditioning [LeDoux, 1998]. These authors conclude that increased 5HT may decrease the sensitivity of the amygdala to activating (particularly aversive) stimuli. [Stutzman et al., 1998]. Others have shown in an in vitro amygdala slice preparation that 5HT mediates this inhibition primarily via activation of $5HT_2$ receptors on inhibitory interneurons within basolateral amygdala [Rainnie, 1999].

Within the amygdala, 5HT may also modulate pathways involving aggression and impulsivity. A range of experiments from mouse gene knockouts [Zhuang et al., 1999] to humans with pathological levels of aggressive behavior [Stanley et al., 2000], suggest that decreased serotonin functioning significantly increases levels of aggression. 5HT decrease in suicide and impulsivity is also highly correlated, suggesting a possible role in modulation of affect and control of impulsive behavioral responsiveness [Mann et al., 1996; Mann 1999].

In addition to its role in neural transmission, there is increasing evidence that 5HT activates neurotrophic factor activity in various brain regions [Azmitia, 1999; Gould, 1999]. There is increasing preclinical evidence for continual, low level neuronal turnover in hippocampus and pre-frontal cortex in adult mammals. In preclinical stress models and in clinical models of depression and chronic anxiety, there is evidence for atrophy and cell death in hippocampus [Bremner et al., 1995; Sheline et al., 1996] as well as prefrontal cortex [Ongur et al., 1998; Rajkowska et al., 1999], that may be mediated by adrenal corticosteroids [McEwen, 1999]. There is recent data that neurogenesis continues into adulthood, providing functioning neurons to hippocampus [Eriksson, 1998] and prefrontal cortex [Gould et al., 1999], but that this neurogenesis is inhibited by stress [Gould et al., 1998; Gould and Tanapat, 1999]. In contrast, 5HT seems to

be a primary activator of adult neurogenesis and axonal and dendritic outgrowth [Gould, 1999]. This may occur due to the influence of 5HT on BDNF production [Duman et al., 1999] and 5HT-mediated release of glial derived growth factors [Azmitia, 1999]. These neurotransmitter systems seem to have opposing roles on cellular homeostasis, with the LC-NE system activating the stress response with corticosteroid production resulting in diminished cell growth and atrophy. In contrast, the RN-5HT system opposes these actions through activation of neurotrophic factor release with increased neurogenesis and process outgrowth.

In summary, 5HT modulates circuitry involved in sleep, appetite, sexual behavior, cognition, and memory. It seems to regulate limbic control of aggression and impulsivity and may mediate tolerance to stressful or fearful stimuli. As opposed to NE that is principally stimulated with behavioral activation toward aversive stimuli, the 5HT system is inhibited by shifting from internally directed repetitive behavior (e.g., grooming) to externally orienting and activating responses. These physiologic studies suggest a role for NE in behavioral activation and vigilance, and in protection via fight or flight responsiveness. In contrast 5HT seems to promote homeostasis via behavioral inhibition and tolerance to aversive stimuli, and via control of behaviors such as sleep, appetite, and sexual behavior.

EVIDENCE FOR A ROLE OF NE AND 5HT IN DEPRESSION AND ANXIETY DISORDERS

There are multiple lines of evidence that the NE and 5HT systems are abnormal in depression and anxiety disorders (see Table 1). Our discussion of these data is by no means comprehensive (there are ~5,000 articles on related topics over the last decade in Medline). Numerous comprehensive reviews have recently been published on this topic [Potter et al., 1993; Schatzberg and Schildkraut 1995; Berman et al., 1996; Leonard, 1997; Charney, 1998; Conner and Davidson, 1998; Nemeroff, 1998; Ninan, 1999; Ressler and Nemeroff, 1999; Sullivan et al., 1999; Delgado and Moreno, 2000]. Rather we focus on some of the most consistent findings in an effort to highlight the role of NE and 5HT in relation to other known abnormalities in depression and anxiety. In total, the data is most consistent that both NE and 5HT systems are dysregulated with depression and anxiety disorders, with more data suggesting increased NE transmission or receptor supersensitivity and decreased 5HT transmission. The data with antidepressant treatment is much more consistent. It suggests that although there may be a broad range of NE and 5HT abnormalities in the depressed and anxious states, the systems are perturbed similarly in most individuals after antidepressant treatment.

NE ALTERATIONS IN DEPRESSION AND ANXIETY DISORDERS

The initial catecholamine hypothesis of affective disorders [Schildkraut, 1965] proposed that abnormally low availability of NE may lead to depressive symptoms, whereas elevated NE availability may lead to euphoric or manic symptoms. After years of research further exploring these relationships, this simple dichotomy is clearly not true. Rather there seems to be a complex dysregulation of NE levels and LC firing in states of depression and anxiety, that may lead to increases or decreases in NE release coupled with altered sensitivities of the pre- and post-synaptic receptors.

Historically, measurement of NE and its metabolites was the most direct window to assess NE functioning. Early reports indicated decreased MHPG levels in urine of depressed patients [Maas et al., 1972]. Further work, however, has shown both increases and decreases in plasma or urinary MHPG levels in patients with depression, often with great variability among patients and studies [Potter et al., 1983; Roy et al., 1986; Potter et al., 1993]. Generally increases in MHPG have been correlated with anxiety [Sevy et al., 1989]. Hypersecretion of NE in plasma and CSF has been reported in unipolar depression and

TABLE 1. Principle evidence for role of norepinephrine and serotonin in mood and anxiety disorders

Alterations in the norepinephrine system in depression/anxiety	**Alterations in the serotonin system in depression/anxiety**
Abnormalities in MHPG levels	Decreased tryptophan concentration
Elevated norepinephrine in plasma and CSF	Reduced CSF 5HT in generalized anxiety disorder
Increased β-adrenergic receptors in post-mortem brain	Decreased 5-HIAA in the CSF
Increased α_2 receptors in post-mortem brain	Increased $5HT_2$ & $5HT_{1A}$ binding in post-mortem cortex
Altered LC neuron density and TH expression	Decreased $5HT_{1A}$ binding in post-mortem limbic areas
Blunted growth hormone response	Decreased serotonin transporter density in platelets
	Blunted prolactin response to fenfluramine
Antidepressant effects on the norepinephrine system	**Antidepressant effects on the serotonin system**
Decreased norepinephrine turnover	Increased serotonin turnover
Decreased β-adrenergic receptor density in animal models	Increased $5HT_{1A}$ density/activity
Overall decrease in NE transmission	**Overall increase in 5HT transmission**

anxiety states [Roy et al., 1988; Sevy et al., 1989; Wyatt et al., 1971], though it is unclear the contribution of the sympathetic nervous system versus CNS NE circuits in these studies.

Measurements of NE receptor kinetics have also been consistently altered in depression and anxiety states. Early recognition of altered α_2 receptor binding in depression and with antidepressant treatment led to the "supersensitivity hypothesis" of α_2 receptors that proposed that supersensitive presynaptic α_2 receptor activity decreased overall LC-NE activity [Charney et al., 1981]; however, these changes could also be seen as evidence that post-synaptic responsiveness to NE in general was supersensitive. Other studies have found increases in α_2 receptors [Meana et al., 1992] and β-adrenergic receptors [Mann et al., 1996; Mann, 1999] as well in post-mortem tissue. This would be consistent with a dysregulation and possibly supersensitivity of NE transmission in depression. An indirect measure of NE transmission and signal transduction is the use of growth hormone (GH) provocative tests with α_2 receptor agonists, that stimulate growth hormone-releasing hormone from hypothalamus. Several groups have reported a markedly blunted GH response to clonidine in patients with depression [Matussek et al., 1980; Siever et al., 1992; Schatzberg and Schildkraut, 1995] and anxiety [Abelson et al., 1991].

Studies of LC number and tyrosine hydroxylase (TH) expression suggest that the LC is profoundly affected in the depressed state. Some studies have found decreased LC neuronal density in depression [Chan-Palay and Asan, 1989; Arango et al., 1996]. Others have not found neuronal density changes, but have shown consistent increases in TH expression [Ordway et al., 1994a] and α_2 receptor density [Ordway et al., 1994b], and decreased NE transporter density [Klimek et al., 1997]. It is unclear whether neuronal number may be decreased initially with later adaptive changes in TH, receptors and transporters, or whether both findings represent evidence of dysregulation, with increased neurotransmission by the remaining LC neurons. In summary, there is a range of variability regarding findings of NE and its metabolites and pre- and postsynaptic adrenergic receptor dynamics. The findings consistently show abnormal NE turnover coupled with likely increased receptor sensitivity. This might suggest that at basal firing conditions, NE levels may indeed be lower than normal, but that rapid LC firing in response to stress may lead to a greater than normal NE transmission due to supersensitive receptors.

5HT ALTERATIONS IN DEPRESSION AND ANXIETY DISORDERS

The serotonin hypothesis of depression suggests that a deficiency of brain serotonergic activity increases vulnerability to depression [Maes and Meltzer, 1995; Mann, 1999]. As with NE, indirect measures of precursor availability and metabolite concentrations provided initial evidence for abnormalities in the system. There are several reports that plasma tryptophan availability is significantly lower in patients with major depression when compared to normal controls [Maes et al., 1990; Deakin et al., 1990]. Although there have been numerous findings of decreased 5HIAA in plasma and CSF in depression [Asberg et al., 1976; Roy et al., 1989], discordant results have also been obtained over the years [Maes and Meltzer, 1995]. CSF 5-HIAA concentrations are more correlated with suicidal and violence-impulsivity behavior than depressive symptoms, per se [Faustman et al., 1991]. Some studies in anxiety disorders have also found decreased 5HT levels in CSF [Brewerton et al., 1995].

As with the NE system in depression and anxiety, there are also alterations in 5HT receptor populations. Increased $5HT_2$ binding [Mann et al., 1986; Arango et al., 1992] and increased $5HT_{1A}$ binding [Matsubara et al., 1991] have been found in cortex in post-mortem tissue, that has been hypothesized to represent upregulation of receptors in the presence of decreased presynaptic transmission. This is subject, however, to the same criticism as above regarding the interaction between suicidality, impulsivity, and depression. One study has found decreased $5HT_{1A}$ density in hippocampus and amygdala [Cheetham et al., 1991], as opposed to increased density in cortex [Matsubara et al., 1991], suggesting differential regulation between limbic and cortical systems. Further evidence for abnormalities in 5HT transmission are the findings of reduced serotonin transporter binding in post-mortem cortex [Leake et al., 1991], though this has not been consistently found [Lawrence, 1993]. A more consistent finding has been reduced serotonin uptake and reduced serotonin transporter binding in platelets [Kaplan and Mann, 1982; Nemeroff, 1988; Owens and Nemeroff, 1994] and more recently in brain [Malison et al., 1998]. Reduced serotonin transporter binding has also been observed in generalized anxiety disorder [Iny et al., 1994].

As with clonidine-induced GH stimulation, the stimulation of prolactin release with fenfluramine, a serotonin mediated event, has been a powerful neuroendocrine challenge test in which to assess serotonergic function. In general, fenfluramine-induced prolactin release is diminished in depressed patients compared to controls [Maes et al., 1990; Lichtenberg et al., 1992]. Furthermore, the blunted prolactin response has been shown to be comparable in patients in remission and with active depression [Flory et al., 1998], suggesting that impaired serotonergic function is a biochemical trait marker that underlies the vulnerability for recurrent episodes of depression [Mann et al., 1995; Mann, 1999].

SUMMARY

Changes in the NE and 5HT systems are well documented in depression and anxiety disorders (see Table 1). Although there is some variability in noradrenergic abnormalities, the combination of increased or de-

creased release with increased or decreased receptor sensitivity suggest that varied mechanisms of dysregulation may lead to the same overall net functional changes. The evidence currently seems more in support of overall increased NE activity in these disorders. In contrast, the data is quite consistent indicating that the 5HT system exhibits overall decreased activity. Different subtypes of these disorders or perhaps genetic vs environmental vulnerability alters the likelihood of pre- vs postsynaptic changes.

Alterations in these systems likely mediate many of the signs and symptoms of depression and anxiety. NE and 5HT modulate subcortical and cortical function such that their dysregulation in states of depression and anxiety contribute to abnormalities in sleep, concentration, attention and memory, arousal states, appetite and libido. Furthermore, their modulation of the cortical-hippocampal-amygdala pathways regulates responses to aversive, stressful, and fearful experience, along with modulation of affective aspects of memory. Abnormal regulation of this pathway may contribute to chronically overactive or hypersensitive stress- and fear-response pathways, along with possibly mediating the features of anxiety, anhedonia, excessive worry, aggression (both internally and externally directed), and affective dyscontrol associated with these disorders.

CHANGES IN THE NE AND 5HT SYSTEMS WITH ANTIDEPRESSANT TREATMENT

Although there are rapid effects of antidepressants on the firing rate and release of neurotransmitter, there is a two to three week lag between initiation of antidepressant treatment and clinical response in both depression and anxiety disorders. Therefore, the alterations in these systems after chronic as opposed to acute antidepressant treatment are obviously key to understanding their function. Despite the at times inconsistent findings in depression and anxiety that implicate complex firing, transporter, and receptor dynamics of both NE and 5HT systems, the changes observed with antidepressant treatment have been more clear and consistent (Table 1).

NE and its metabolites are clearly decreased in CSF after chronic administration of both noradrenergic and serotonergic antidepressants [Javaid et al., 1983; Potter et al., 1985; DeBellis et al., 1993]. Furthermore decreased LC firing has been reproduced extensively with chronic antidepressant treatment [Huang et al., 1980; Svensson, 1980; Mongeau et al., 1997]. Down regulation of the β-adrenergic receptors has also been a consistent finding with different antidepressant treatments and ECT [Vetulani and Sulser, 1975; Brunello, 1982; Stanford and Nutt, 1982; Duncan, 1989]. Decreased TH activity and TH mRNA have suggested decreased NE production with chronic antidepressant treatment [Nestler et al., 1990; Brady et al., 1991; Melia et al., 1992]. Thus it has become increasingly accepted that long-term antidepressant treatment is associated with, and may depend upon, decreasing transmission of the locus coeruleus norepinephrine system [Nestler et al., 1990; Schatzberg and Schildkraut, 1995; Mongeau et al., 1997; Owens, 1997; Delgado and Moreno, 2000].

As opposed to NE, the raphe 5HT system seems to exhibit increased activity after chronic antidepressant treatment. Increased 5HT levels in forebrain and raphe have been shown by microdialysis with chronic antidepressant treatment [Bel and Artigas, 1993; Blier and Bouchard, 1994]. Increased prolactin responsiveness to tryptophan [Price et al., 1991] and fenfluramine challenge [O'Keane et al., 1992] also occurs after chronic antidepressant treatment, suggesting enhanced pre-or postsynaptic 5HT activity [Maes and Meltzer, 1995]. Increased density and sensitivity of the postsynaptic $5HT_{1A}$ receptors has been shown with antidepressant treatment and ECT, suggesting increased efficacy of the 5HT pathway [deMontigny and Aghajanian. 1978; Dijcks et al., 1991; Hayakawa et al., 1993]. Finally, decrease in 5HT reuptake transporter density and sensitivity has been shown with chronic antidepressant treatment [Lesch et al., 1993; Owens and Nemeroff, 1994; Pineyro et al., 1994], suggesting increased synaptic concentrations of 5HT. Thus it has become increasingly accepted that long-term antidepressant treatment is associated with, and may depend upon, increasing transmission of the raphe nuclei serotonin system [Maes and Meltzer, 1995; Mongeau et al., 1997; Nemeroff, 1998; Owens, 1997; Mann, 1999].

It is initially counterintuitive that the alterations in overall NE and 5HT activity would shift in opposite directions with antidepressant treatment. Interestingly, these shifts seem to occur in both systems whether the treatment is 5HT reuptake specific, NE reuptake specific, dual reuptake blockade, or ECT. These changes suggest that there are changes that occur associated with treatment of depression that alter both NE and 5HT neuromodulatory systems, in addition to other interacting systems (vida infra). A comprehensive review of NE and 5HT systems in the context of hippocampal activity by deMontigny et al. [1997] addresses the data contributing to the hypothesis of decreased noradrenergic and increased serotonergic activity with antidepressant treatment. The combination of $5HT_{1A}$ autoreceptor desensitization, α_2 autoreceptor sensitization, and βAR desensitization all result in a net increase in $5HT_{1A}$ post-synaptic transmission and a net decrease in βAR activation. They suggest that through a combination of alterations in receptor regulation and interactions between the excitatory NE and inhibitory 5HT systems, antidepressants act by reducing NE transmission and increasing 5HT transmission.

DEPLETION STUDIES SUGGEST DEPENDENCE OF ANTIDEPRESSANT TREATMENT ON TRANSMITTER AVAILABILITY

Despite the apparent similarity of NE or 5HT acting antidepressants on the NE and 5HT systems, it has been clearly demonstrated that serotonergic-specific or noradrenergic-specific antidepressants are dependent on the availability of 5HT and NE, respectively, for their antidepressant efficacy [Charney, 1998]. Furthermore, rapid depletion of 5HT, but not NE, induces rapid relapse in depressed patients during serotonergic antidepressant-induced remission [Delgado and Moreno, 2000]. Conversely, the opposite is true for depressed patients during noradrenergic antidepressant-induced remission. Normal control subjects and patients in complete remission and drug free, however, do not seem to be sensitive to monoamine depletion [Henninger et al., 1996]. Monamines thus must play a critical role in modulating other neurobiologic systems involved in recovery from depression, rather than represent the primary cause of depression.

OTHER FINDINGS IN DEPRESSION AND ANXIETY DISORDERS

This review has focused on the NE and 5HT systems. As noted above, however, there is increasing evidence that these systems regulate other neural circuits, and that it is increasingly unlikely that the etiology of mood and anxiety disorders lies within the monoaminergic neurons themselves. Therefore, a brief review of other systems altered in depression and modulated by antidepressant treatment may suggest interactions between these other neural systems and monoamine circuits.

NEUROIMAGING

Functional imaging experiments with positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided new insights into the neural circuits involved in the pathophysiology of depression. Numerous studies have found changes in frontal cortical activity in depressed states [Drevets, 1998; Mayberg et al., 1999]. In these studies, there seems to be differential activation of cortex. Dorsal prefrontal cortical (PFC) activity is generally suppressed [Dolan et al., 1993, 1994; Biver et al., 1994; Drevets, 1998], in contrast to ventral PFC and orbital cortex that have been found to be activated in depressed patients when compared to controls [Baxter et al., 1987; Drevets et al., 1992; Price et al., 1996]. The increased activation of ventral and orbital areas is also found in anxiety disorders including obsessive-compulsive disorder [Baxter et al., 1987; Rauch et al., 1994]. Antidepressant treatment normalizes both of these abnormalities, increasing dorsal PFC activity, and decreasing ventral PFC and orbital activity. The amygdala has been consistently abnormally activated in depression studies [Drevets, 1998], with its imaged activity correlating with depression severity [Drevets et al., 1992, 1995; Abercrombie et al., 1996]. As with the cortical abnormalities, the amygdala activity decreases toward normal with antidepressant response and remission [Drevets, 1998].

STRESS HORMONES

In addition to monoamine abnormalities in depression, there is equally impressive literature on the role of hyperactivity of neurons that utilize corticotropin releasing factor (CRF) in depression [reviewed in Nemeroff, 1996; Plotsky et al., 1998; Heim and Nemeroff, 1999]. Amygdala activation of the fear-stress response circuitry leads to activation of the central nucleus of the amygdala [Davis, 1998a; LeDoux, 1998] or the bed nucleus of the stria terminalis (BNST), a similar region of the 'extended amygdala' thought to be important in anxiety symptoms [Davis, 1998b]. With such activation, numerous pathways mediating the fear-stress response are initiated (Table 2), [Davis, 1998a], leading to CRF release in numerous brain areas thereby mobilizing the CNS response to stress [Nemeroff, 1996]. In addition, direct activation of the paraventricular nucleus (PVN) of the hypothalamus leads to CRF release that stimulates the secretion of ACTH from the anterior pituitary gland. CRF has repeatedly been reported to be elevated in the CSF of patients with depression [Nemeroff et al., 1984; Plotsky et al., 1998]. Up to 75% of patients with major depression have an overactive HPA axis as characterized

TABLE 2. Limbic system control of emotional response*

Central nucleus of amygdala/BNST efferent pathway	Stress/fear response
Paraventricular nucleus of hypothalamus	CRF/HPA axis activation
Lateral hypothalamus	Sympathetic activation
Nucleus ambiguous/DMN of vagus	Parasympathetic activation
Parabrachial nucleus	Dyspnea, hyperventilation, somatic symptoms
VTA/Locus coeruleus	Hyperarousal, vigilance, stress responsivity
Nucleus reticularis pontis caudalis	Increased startle response
Midbrain central gray	Freezing, inactivity, fear of dying
Trigeminal/facial motor nerve	Facial expression of negative affect

**Adapted from Davis, 1998a.*

by hypercortisolemia [Laird and Benefield, 1995; Nemeroff, 1998; Ninan, 1999]. HPA axis dysfunction has also been reported in some cases of generalized anxiety disorder, as evidenced by dexamethasone suppression test results [Avery et al., 1985; Tiller et al., 1988]. Although in most studies of panic disorder, there are no clear chronic abnormalities of HPA function, pretreatment dysfunction of the HPA axis is correlated with poorer prognosis [Abelson and Curtis, 1996]. Evidence of significant alterations in CRF neuronal density [Raadsheer et al., 1994] and increased mRNA expression [Raadsheer et al., 1995] suggest that depression involves a state of significantly altered neural circuitry mediating the stress response pathways. Consistent with data discussed in the preceding paragraph, neuroimaging studies show correlation between increased amygdala activation and plasma cortisol levels in depression [Abercrombie et al., 1996; Drevets, 1997]. Furthermore, there is clear evidence for dysregulation of the NE and CRF systems in models of developmental stress with later onset of depression and anxiety symptoms in adulthood [Francis et al., 1999; Koob, 1999].

NEUROTROPHIC FACTORS

A burgeoning database now supports the hypothesis that stress, depression, and perhaps certain anxiety disorders are associated with degeneration of target neurons, perhaps mediated by cortisol hypersecretion [Duman et al., 1999; McEwen, 1999]. Hippocampal atrophy and adrenal hypertrophy have been observed in numerous studies of depression and anxiety related disorders [Bremner, 1995; Sheline et al., 1996; Gould et al., 1998]. Glial cell loss and neuronal abnormalities have been found in prefrontal cortex in major depression [Ongur et al., 1998; Rajkowska et al., 1999]. Noradrenergic axons have been found with decreased axonal arborization and density in stress models [Kitayama et al., 1994, 1997]. Serotonergic axon sprouting seems to be dependent on BDNF [Mamounas et al., 1995], that seems to be decreased with stress and perhaps in depression [Duman et al., 1999]. Therefore, stress and disorders related to chronic stress seem to increase neuronal atrophy and degeneration. In contrast, it seems that hippocampal neurons undergo continued proliferation well into adulthood, and that this continued neurogenesis may be dependent on the presence of serotonin [Azmitia, 1999; Gould, 1999] and inhibited by adrenal steroids [McEwen, 1999]. Antidepressant treatment seems to at least partially reverse or block the atrophy of hippocampal neurons, increases cell survival and increases monoamine axonal sprouting [Duman et al., 1999; McEwen, 1999 and H. Manji, personal communication].

NE AND 5HT REGULATION OF NEURAL SYSTEMS INVOLVED IN DEPRESSION AND ANXIETY DISORDERS

As more data are generated regarding abnormalities in various brain systems in depression and anxiety, the field is moving from separate competing non-overlapping theories toward a convergence of views, in which the different systems are interacting and interdependent. The brainstem monoamine systems seem to have significant modulatory roles in regulating these other systems. Figure 1 summarizes the pathways discussed below and the proposed changes in depression and anxiety.

The limbic circuitry mediating stress, fear, anger, and other emotions seems to be central to both depression and anxiety disorders. In normal functioning, the role of the amygdala seems to be the continuous monitoring of sensory thalamic and cortical stimuli in relationship to previously learned aversive stimuli (fear/stress/pain mediating) or appetitive stimuli (approach/motivational/hedonic mediating) [Lang et al., 1998]. Recognition of previous associations would activate the appropriate conditioned response pathway (e.g., central nucleus of amygdala–stress/fear responses, BNST fear/anxiety responses, nucleus accumbens–appetitive/approach responses) [LeDoux, 1996]. Central nucleus activation would initiate a host of neural and endocrine stress responses (see Table 2) including CRF release in many areas and eventual adrenal cortisol release [Davis, 1998a]. In parallel with this pathway, the hippocampus is thought to provide a dual role in contextual memory functioning. During low stress, the hippocampus attenuates the amygdala response and potentiates extinction of aversive memories, whereas during periods of higher stress or alertness, the hippocampus increases LTP related to aversive contexts and potentiates amygdala responsiveness [Gray, 1987; Mongeau et al., 1997]. Prefrontal cortex, with its highly refined information has significant interconnectivity with the amygdala [McDonald, 1998]. Extinction of aversive memories clearly requires cortical input [Morgan et al., 1993]. This is consistent with the idea that higher order representations are able to modulate lower order associations—that rational thought should prevail over irrational fear or worry. It has been proposed that the prefrontal cortex is involved via these connections in regulating affect, providing cognitive control over stress and fear responsiveness along with anger, anxiety, and frustration tolerance [Lang et al., 1998; LeDoux, 1996].

The LC shows greatest activation in orienting to novel, aversive, or stressful stimuli [Robbins and Everitt, 1995]. NE from the LC stimulates potentially stressful memories and fear/stress responses in the amygdala [Cahill and McGaugh, 1998]. NE also increases LTP and contextual conditioning to aversive stimuli in hippocampus [Mongeau, 1997]. This is consistent with the role of the LC-NE system in vigilance and survival via activation of fight-flight response. CRF release with amygdala activation leads to an activation of LC firing, and NE has also been shown to directly activate CRF activity in the amygdala [Feldman and Weidenfeld, 1998; Van Bockstaele et al., 1999]. Furthermore, NE activation of cortex is com-

plex, with decreased activation at too low or too high levels of release, and optimal activation with midrange firing. Thus at high rates of activity, NE could potentially lead to an overactivation of the limbic stress/fear pathways over cortical pathways, as presumably would promote survival if rapid fight or flight response is needed [Valentino et al., 1993]. Finally, LC-NE activation seems to have an inhibitory role on the RN-5HT system [Mongeau et al., 1997].

The RN show highest firing during internally directed, rhythmic movements and behaviors, with diminished firing when orienting to external stimuli [Jacobs and Fornal, 1999]. 5HT from the raphe nuclei mediates tolerance to aversive experience in the amygdala, potentially decreasing the likelihood of a fight or flight response [Stutzmann et al., 1998]. It seems to decrease context conditioning in hippocampus with aversive stimuli, and is hypothesized to provide tolerance to aversive contexts [Mongeau et al., 1997]. These roles are consistent with the role of the raphe-5HT system in homeostasis, decreased aggression, and tolerance to aversion. Raphe firing is inhibited by LC-NE activation, and also by ventral or orbital cortex activation [Hajos et al., 1998]. These regions of cortex have been shown to be activated in correlation with sad or stressful emotion, and are thought to be important in control over amygdala activation [Drevets, 1998; Cahill and McGaugh, 1998]. Furthermore, regions of prefrontal cortex that have been shown to be modulated by amygdala during conditioned fear [Garcia et al., 1999] are also clearly important in mediating extinction to aversive memories [Morgan and LeDoux, 1995]. Production of new neurons in the hippocampus and prefrontal cortex, along with dendritic and axonal arborization seem to be promoted by normal 5HT release, and inhibited by excess adrenal cortisol levels [Gould, 1999; McEwen, 1999].

NORMAL RESPONSE TO STRESS

The LC-NE system and the RN-5HT system can be thought of as modulatory systems that exhibit baseline tonic firing, and that are exquisitely controlled by other neural pathways and complex regulatory loops. During normal functioning, in safe conditions when internally directed behaviors such as feeding or grooming prevail, the RN are relatively uninhibited and serve to inhibit the LC and limbic pathways leading to decreased sensitivity to arousal or stressful/aversive stimuli (Fig. 1, Euthymic). During such states, higher cortical centers prevail over limbic control of affect. Furthermore, neuronal homeostatic mechanisms prevail, with decreased cortisol secretion and increased 5HT-mediated neurotrophic factor release activating neuronal growth and neuronal process extension. When the organism is stressed, however, the balance shifts. The recognition of potentially stressful/aversive stimuli by amygdala pathways activates LC firing, that then inhibits RN firing. LC activation of amygdala-hippocampal pathways increases the sensitivity to and memory of stressful/aversive stimuli further increasing CRF and cortisol secretion. These combined shifts lead limbic pathways to prevail over prefrontal cortical pathways in the control of affect. The organism is then primed in a state of arousal or vigilance to prepare for initiation of the fight or flight stress response. In the normal or euthymic state, however, the organism can return to a baseline affective response state when the stressful/aversive stimulus is removed.

ABNORMAL REGULATION DURING DEPRESSED AND ANXIETY STATES

In the depressed and in some anxiety states, the system described above is dysregulated (Fig. 1, Depression). NE transmission is overactive via LC firing, receptor sensitivity, or both. Of note, NE transmission need not be tonically overactive, in fact a similar outcome may be seen with a lowered basal firing rate but abnormally high receptor sensitivity to increased LC-NE activity during stress. In contrast, 5HT transmission is underactive via inhibited RN firing, decreased receptor sensitivity or both. These neurotransmitter alterations contribute to overactivation of amygdala, hippocampal and cortical pathways activating stress/fear responsiveness, and to underactivation of higher cortical areas involved in inhibiting these pathways. Ventral cortical areas primarily associated with affect and strongly interconnected with amygdala are also overactivated and may contribute to inhibition of RN firing. Abnormally activated central amygdala and BNST lead to increased release of CRF and adrenal steroids together with increased activity of autonomic, visceral, and neural pathways associated with stress/fear responsiveness. These systems in turn serve to further activate the LC-NE system promoting vigilance and stress/fear responsiveness. In these psychopathological states, the same intensity of stressful stimulus that might only lead to minimally increased arousal in the normal "euthymic" system, might lead to significant arousal, vigilance and activation of the fight or flight and anxiety response pathways.

Chronic levels of elevated adrenal glucocorticoids secondary to elevated CRF activation contributes to hippocampal and cortical atrophy. Decreased neuronal density and atrophy in the hippocampus presumably contributes to decreased hippocampal activity, possibly decreasing its ability to inhibit amygdala stress/fear responsiveness. Atrophy in the prefrontal cortex likely decreases the ability of cortical modulation and inhibition of amygdala aversion pathways. Decreased 5HT release may also contribute to this neuronal degeneration, dendritic atrophy, and lack of regeneration by diminished neurotrophic factor release. Together, these processes likely serve to maintain the state of imbalance by decreasing the ability of cortical and hippocampal areas to inhibit and modulate the stress/fear pathways of the amygdala and interconnected circuitry. The depressed or anxious state is one in which

these stress/fear pathways cannot be easily 'shut off' or returned to normal, and the individual is left in a chronic state of abnormal affective responsiveness.

ADAPTATION AND RESTORATION OF FUNCTION WITH ANTIDEPRESSANT TREATMENT

Through mechanisms mentioned above, primarily 5HT, NE, and dual 5HT/NE antidepressants seem to reset the dysregulated system in similar ways. In general, 5HT and NE neurotransmission is increased and decreased, respectively. These shifts seem to reset the system leading to decreased amygdala hyperactivity, increased tolerance to aversion, and increased cortical control over affective response and stress/fear responsiveness. ECT seems to have similar chronic effects on the system, possibly via strengthening the prefrontal cortex connectivity with limbic structures as a consequence of seizure activity. It has been proposed that psychotherapy might have similar effects on the system, via increasing cognitive/cortical control over limbic pathways [LeDoux, 1996]. Shifting the balance of NE and 5HT activity would also result in decreased adrenal steroid and increased neurotrophic factor activity, slowly increasing neuronal density and process growth. The slow time course of antidepressant response may reflect the combined time courses of the relatively early adaptation of monoamine transmission and receptor sensitivity, the later increases in strength of cortical modulation of amygdala, and the delayed increases in neurotrophic factor-mediated neuronal growth and arborization. These prolonged changes may serve to stabilize the system in a new state without the continued presence of antidepressant.

CONCLUSIONS

The NE and 5HT systems play crucial roles in mediating the affective circuitry underlying the highly related clinical disorders of depression and anxiety. There is a clear dysregulation of NE and 5HT activity contributing to these illnesses. As understanding of neurobiology has broadened, however, their roles have become more complex. Initially postulated to be the causal abnormalities mediating these abnormal affective states, they are now recognized as complex modulators of multiple circuits that together regulate affective tone along with the neurovegetative and autonomic symptoms associated with these disorders.

The roles of genetics, development, and stress contributing to illness are becoming understood in terms of the biology of the brain. Temperamental influences clearly place 'reactive' infants and behaviorally inhibited children at higher risk in adulthood for anxiety and affective disorders [Kagan and Snidman, 1999]. Furthermore, a large body of data now supports the preeminent influence of early adverse experience in increasing the vulnerability for later mood and anxiety disorders [Heim and Nemeroff, 1999]. These genetic predispositions and environmental influences likely act upon the neural circuits that mediate stress/fear responsiveness and affect modulation. The alterations in limbic CRF systems and brainstem NE and 5HT systems likely contribute to these increased vulnerabilities. With sufficient stress, these systems likely shift to a dysregulated state leading to increased stress and fear responsiveness, along with impaired cortical modulation of affective tone. These hypersensitive limbic pathways likely lead to experiences of defeat, anxiety, anger, negative mood, and aggression. Abnormal cortical regulation likely mediates impaired concentration and memory, worry, and inability to control negative thoughts. Hypothalamic abnormalities contribute to altered appetite, libido, energy, autonomic symptoms, and possibly somatic symptoms. Brainstem and thalamic abnormalities contribute to altered sleep and arousal states.

Antidepressant therapies remain focused on shifting the NE/5HT balance, yet a further understanding of the interacting systems that likely mediate and maintain the depressed or anxious state will advance approaches to treatment. For example, other effective interventions might be viewed in the framework of such network models, e.g., ECT may alter limbic and cortical-limbic interaction, psychotherapy might increase cortical modulation of limbic pathways, and vagus nerve stimulation might alter limbic NE release via NST. Undoubtedly, the understanding of the pathophysiology and treatment of mood and anxiety disorders will continue to rapidly expand as the relationship among specific neurotransmitter systems and the complex neural circuitry mediating behavior is more fully understood.

REFERENCES

Abelson JL, Glitz D, Cameron OG, Lee MA, Bronzo M, Curtis GC. 1991. Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. Arch Gen Psychiatry 48:157–162.

Abelson J, Curtis G. 1996. Hypothalamic-pituitary-adrenal axis activity in panic disorder: predictor of long-term outcome by pretreatment cortisol levels. Am J Psychiatry 153:69–73.

Abercrombie H, Larson C, Ward R, et al. 1996. Metabolic rate in the amygdala predicts negative affect and depression severity in depressed patients: an FDG-PET study. Neuroimage 3:S217.

Aghajanian G. 1995. Electrophysiology of serotonin receptor subtypes and signal transduction pathways. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 451–460.

Aghajanian G, Marek G. 1999. Serotonin and hallucinogens. Neuropsychopharmacology 21:16S–23S.

Amara S, Kuhar M. 1993. Neurotransmitter transporters: recent progress. Ann Rev Neurosci 16:73–93.

Arango V, Underwood M, Mann J. 1992. Alterations in monoamine receptors in the brain of suicide victims. J Clin Psychopharmacol 12:8–12.

Arango V, Underwood M, Mann J. 1996. Fewer pigmented locus

coeruleus neurons in suicide victims: preliminary results. Biol Psychiatry 39:112–120.

Arborelius L, Owens M, Plotsky P, Nemeroff C. 1999. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol 160:1–12.

Asberg M, Traskman L, Thoren P. 1976. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch Gen Psychiatry 33:1193–1197.

Ashby C, Jiang L, Kasser R, Wang R. 1990. Electrophysiological Characterization of 5-HT_2 receptors in the rat medial prefrontal cortex. J Pharm Exp Ther 252:171–178.

Aston-Jones G, Chiang C, Alexinsky T. 1991a. Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. Prog Brain Res 88:501–520.

Aston-Jones G, Shipley M, Chouvet G, et al. 1991b. Afferent regulation of locus coeruleus neurons: anatomy, physiology and pharmacology. Prog Brain Res 85:47–75.

Avery D, Osgood T, Ishiki D, Wilson LG, Kenny M, Dunner DL. 1985. The DST in psychiatric outpatients with generalized anxiety disorder, panic disorder, or primary affective disorder. Am J Psychiatry 142:844–848.

Azmitia E. 1999. Serotonin neurons, neuroplasticity, and homeostasis of neural tissue. Neuropsychopharmacology 21:33S–45S.

Baxter L, Phelps M, Mazziotta J, Guze BH, Schwartz JM, Selin CE. 1987. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in depression and in normal controls. Arch Gen Psychiatry 44:211–218.

Bel N, Artigas F. 1993. Chronic treatment with fluvoxamine increases extracellular serotonin in frontal cortex but not in raphe nuclei. Synapse 15:243–245.

Berman R, Krystal J, Charney D. 1996. Mechanism of action of antidepressants: monoamine hypotheses and beyond. In: Watson S, editor. Biology of schizophrenia and affective disease. Washington, DC: American Psychiatric Press, Inc. p 295–368.

Biver F, Goldman S, Delvenne V, Luxen A, De Maertelaer V, Hubain P, Mendlewicz J, Lotstra F. 1994. Frontal and parietal metabolic disturbances in unipolar depression. Biol Psychiatry 36:381–388.

Blier P, Bouchard C. 1994. Modulation of 5HT release in the guinea pig brain following long-term administration of antidepressant drugs. Br J Pharmacol 113:485.

Brady L, Whitfield H Jr, Fox RJ, Gold PW, Herkenham M. 1991. Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. Therapeutic implications. J Clin Invest 87:831–837.

Bremner J, Randall P, Scott T, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. 1995. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 152:973–981.

Brewerton T, Lyiard R, Johnson M, et al. 1995. CSF serotonin: Diagnostic and seasonal differences. New Research and Abstracts of the 148th Meeting of the American Psychiatric Association. Washington DC: American Psychiatric Press. Abstract NR385:151.

Brunello N, Barbaccia M, Chuang D, Costa E. 1982. Down-regulation of β-adrenergic receptors following repeated injections of desmethylimipramine, permissive role of serotonergic axons. Neuropharmacology 21:1145–1149.

Buhot M. 1997. Serotonin receptors in cognitive behaviors. Curr Opin Neurobiology 7:243–254.

Cahill L, McGaugh J. 1998. Mechanisms of emotional arousal and lasting declarative memory. TINS 21:294–299.

Chan-Palay V, Asan E. 1989. Quantitation of catecholamine neurons in the locus coeruleus in human brains of normal young and older adults and in depression. J Comp Neurol 287:357–372.

Charney D, Heninger G, Sternberg D, Redmond DE, Leckman JF, Maas JW, Roth RH. 1981. Presynaptic adrenergic receptor sensitivity in depression: the effect of long-term desipramine treatment. Arch Gen Psychiatry 38:1334–1340.

Charney D. 1998. Monoamine dysfunction and the pathophysiology and treatment of depression. J Clin Psychiatry 59(Suppl):11–14.

Chauloff F, Berton O, Mormede P. 1999. Serotonin and stress. Neuropsychopharmacology 21:28S–32S.

Cheetham S, Crompton M, Katona C, Horton RW. 1990. Brain 5HT1 binding sites in depressed suicides. Psychopharmacology 102:544–548.

Connor K, Davidson J. 1998. Generalized anxiety disorder: neurobiological and pharmacotherapeutic perspectives. Biol Psychiatry 44:1286–1294.

Curet O, deMontigny C. 1988. Electrophysiological characterization of adrenoceptors in the rat dorsal hippocampus I. Receptors mediating the effect of microiontophoretically applied norepinephrine. Brain Res 475:35–46.

Davis M. 1998a. Anatomic and physiologic substrates of emotion in an animal model. J Clin Neurophysiol 15:378–387.

Davis M. 1998b. Are different parts of the extended amygdala involved in fear vs. anxiety. Biol Psychiatry 44:1239–1247.

Deakin J, Pennell I, Upadhyaya A, Lofthouse R. 1990. A neuroendocrine study of 5HT function in depression: evidence for biological mechanisms of endogenous and psychosocial causation. Psychopharmacology 101:85–92.

DeBellis M, Geracioti T, Altemus M, Kling MA. 1993. Cerebrospinal fluid monoamine metabolites in fluoxetine-treated patients with major depression and in healthy volunteers. Biol Psychiatry 33:636–641.

Delgado P, Moreno F. 2000. Role of norepinephrine in depression. J Clin Psychiatry 61(Suppl):5–12.

deMontigny C, Aghajanian G. 1978. Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. Science 202:1303–1306.

DeParmentier F, Cheetham S, Crompton M, Katona CL, Horton RW. 1990. Brain β-adrenoceptor binding sites in anti-depressant-free depressed suicide victims. Brain Res 525:71–77.

Dijcks F, Ruight G, DeGraaf J. 1991. Antidepressants affect amine modulation of neurotransmission in the rat hippocampal slice. Delayed effects. Neuropharmacology 30:1141–1150.

Dolan R, Bench C, Liddle P, Friston KJ, Frith CD, Grasby PM, Frackowiak RS. 1993. Dorsolateral prefrontal cortex dysfunction in the major psychoses: symptom or disease specificity? J Neurol Neurosurg Psychiatry 56:1290–1294.

Dolan R, Bench C, Brown R, Scott LC, Frackowiak RS. 1994. Neuropsychological dysfunction in depression: the relationship to regional cerebral BF. Psychiatric Med 24:849–85y.

Drevets W, Videen T, Price J, et al. 1992. A functional anatomical study of unipolar depression. J Neurosci 12:3628–3641.

Drevets W, Spitznagel E, Raichle M. 1995. Functional anatomical differences between major depressive subtypes. J Cereb Blood Flow Metab 15:S93.

Drevets W, Price J, Simpson J Jr, Todd RD, Reich T, Vannier M, Raichle ME. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386:824–827.

Drevets W. 1998. Functional neuroimaging studies of depression: the anatomy of melancholia. Ann Rev Med 49:341–361.

Duman R, Malberg J, Thome J. 1999. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 46:1181–1191.

Duncan G, Paul I, Powell K, Fassberg JB, Stumpf WE, Breese GR. 1989. Neuroanatomically selective down-regulation of β-adrenergic receptors by chronic imipramine treatment: relationships

to the topography of [^{3}H]imipramine and [^{3}H]desipramine binding sites. J Pharmacol Exp Ther 248:470–477.

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. 1998. Neurogenesis in the adult human hippocampus. Nat Med 4:1313–1317.

Faustman WO, King RJ, Faull KF, Moses JA Jr, Benson KL, Zarcone VP, Csernansky JG. 1991. MMPI measures of impulsivity and depression correlate with CSF 5-HIAA and HVA in depression but not schizophrenia. J Affect Disord 22:235–239.

Feldman S, Weidenfeld J. 1998. The excitatory effects of the amygdala on hypothalamo-pituitary-adrenocortical responses are mediated by hypothalamic norepinephrine, serotonin, and CRF-41. Brain Res Bull 45:389–393.

Flory J, Mann J, Manuck S, Muldoon M. 1998. Recovery from major depression is not associated with normalization of serotonergic function. Biol Psychiatry 43:320–326.

Foote S, Aston-Jones G. 1995. Pharmacology and physiology of central noradrenergic systems. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 335–345.

Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ. 1999. The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol Psychiatry 46:1153–1166.

Frazer A, Hensler J. 1994. Serotonin. In: Siegel G, Agranoff B, Albers R, Molinoff P, editors. Basic neurochemistry, 5th edition. New York: Raven Press, Ltd. p 283–308.

Freis E. 1954. Mental depression in hypertensives treated for long periods with large doses of reserpine. N Engl J Med 251:1006–1008.

Garcia R, Vouimba R, Baudry M, Thompson R. 1999. The amygdala modulates prefrontal cortex activity relative to conditioned fear. Nature 402:294–296.

Glennon R, Dukat M. 1995. Serotonin receptor subtypes. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 415–429.

Gould E, Tanapat P, McEwen B, et al. 1998. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci 95:3168–3171.

Gould E, Reeves A, Graziano M, Gross C. 1999. Neurogenesis in the neocortex of adult primates. Science 286:548–552.

Gould E, Tanapat P. 1999. Stress and hippocampal neurogenesis. Biol Psychiatry 36:1472–1479.

Gould E. 1999. Serotonin and hippocampal neurogenesis. Neuropsychopharmacology 21:46S–51S.

Gray J. 1987. The neuropsychology of anxiety: an inquiry into the functions of the septo-hippocampal system. Oxford: Oxford University Press.

Gulley LR, Nemeroff CB. 1993. The neurobiological basis of mixed depression-anxiety states. J Clin Psychiatry 54(Suppl):16–19.

Gurevich E, Joyce J. 1996. Comparison of [^{3}H]paroxetine and [^{3}H]cyanoimipramine for quantitative measurement of serotonin transporter sites in human brain. Neuropsychopharmacology 14:309–323.

Hajos M, Richards C, Szekely A, Sharp T. 1998. An electrophysiological and neuroanatomical study of the medial prefrontal cortical projection to the midbrain raphe nuclei in the rat. Neuroscience 87:95–108.

Hayakawa H, Yokota N, Kawai K, Okamoto Y, Osada M, Kikumoto O, Motohashi N, Yamawaki S, Nishida A, Shimizu M. 1993. Effects of electroconvulsive shock on the scrotonin metabolism and serotonin 1A receptors in the rat brain. Jpn J Psychiatry Neurol 47:418–419.

Heim C, Nemeroff C. 1999. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. Biol Psychiatry 46:1509–1522.

Heninger G, Delgado P, Charney D. 1996. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry 29:2–11.

Hopkins W, Johnston D. 1988. Noradrenergic enhancement of long-term potentiation at mossy fiber synapses in the hippocampus. J Neurophysiol 59:667–687.

Hoyer D, Martin G. 1997. 5HT receptor classification and nomenclature: toward a harmonization with the human genome. Neuropharmacology 36:419–428.

Huang Y, Maas J, Hu G. 1980. The time course of noradrenergic pre- and postsynaptic activity during chronic desipramine treatment. Eur J Pharmacol 68:41–47.

Iny L, Pecknold J, Suranyi-Cadotte B, Bernier B, Luthe L, Nair NP, Meaney MJ. 1994. Studies of a neurochemical link between depression, anxiety, and stress from [^{3}H]imipramine and [^{3}H]paroxetine binding on human platelets. Biol Psychiatry 36:281–291.

Jacobs B, Fornal C. 1995. Serotonin and behavior: a general hypothesis. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 461–769.

Jacobs B, Fornal C. 1999. Activity of serotonergic neurons in behaving animals. Neuropsychopharmacology 21:9S–15S.

Javaid J, Rubinstien J, Davis J. 1983. Effects of pharmacological agents on MHPG. In: Maas J, editor. MHPG: basic mechanisms and psychopathology. New York: Academic Press. p 45–67.

Kagan J, Snidman N. 1999. Early childhood predictors of adult anxiety disorders. Biol Psychiatry 46:1536–1541.

Kaplan R, Mann J. 1982. Altered platelet serotonin uptake kinetics in schizophrenia and depression. Life Sci 3:583–588.

Kasamatsu T, Itakura T, Johnson G, et al. 1984. Neuronal plasticity in cat visual cortex: a proposed role for the central noradrenaline system. In: Descarries L, Reader T, Jasper H, editors. Monoamine innervation of cerebral cortex. New York: Alan R. Liss, Inc. p 301–320.

Kessler RC, Nelson CB, McGonagle KA, et al. 1996. Comorbidity of DSM-IIIR major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psych 168(Suppl) :17–30.

Kitayama I, Nakamura S, Yaga T, Murase S, Nomura J, Kayahara T, Nakano K. 1994. Degeneration of locus coeruleus axons in stress-induced depression model. Brain Res Bull 35:573–580.

Kitayama I, Yaga T, Kayahara T, Nakano K, Murase S, Otani M, Nomura J. 1997. Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. Biol Psychiatry 42:687–696.

Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA. 1997. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 17: 8451–8458.

Koob GF. 1999. Corticotropin-releasing factor, norepinephrine, and stress. Biol Psych 46:1167–1180.

Laird L, Benefield W. 1995. Mood disorders. I: major depressive disorders. In: Young L, Koda-Kimble M, editors. Applied therapeutics: the clinical use of drugs. Vancouver: Applied Therapeutics Inc. p 1–28.

Lang P, Bradley M, Cuthbert B. 1998. Emotion, Motivation, and Anxiety: Brain Mechanisms and Psychophysiology. Biol Psychiatry 44:1248–1263.

Lawrence K, Falkowski J, Jacobson R, Horton R. 1993. Platelet 5HT uptake sites in depression—3 concurrent measures using [^{3}H]-imipramine and [^{3}H]-paroxetine. Psychopharmacology 110:235–239.

Leake A, Fairbairn A, McKeith I, Ferrier I. 1991. Studies on the serotonin uptake binding site in major depressive disorder and control post-mortem brain: neurochemical and clinical correlates. Psychiatr Res 39:155–165.

LeDoux J. 1996. The emotional brain: the mysterious underpinnings of emotional life. New York: Simon and Schuster. p 225–266.

LeDoux J. 1998. Fear and the brain: where have we been, and where are we going? Biol Psychiatry 44:1229–1238.

Leonard B. 1997. The role of noradrenaline in depression: a review. J Psychopharm 11(Suppl):S39–S47.

Lesch K, Aulakh C, Wolozin B, Tolliver TJ, Hill JL, Murphy DL. 1993. Regional brain expression of serotonin transporter mRNA and its regulation by reuptake inhibiting antidepressants. Mol Brain Res 17:31–35.

Levitt P, Rakic P, Goldman-Rakic P. 1984. Comparative assessment of monoamine afferents in mammalian cerebral cortex. In: Descarries L, Reader T, Jasper H, editors. Monoamine innervation of cerebral cortex. New York: Alan R. Liss, Inc. p 41–60.

Lichtenberg P, Shapira B, Gillon D, Kindler S, Cooper TB, Newman ME, Lerer B. 1992. Hormone responses to fenfluramine and placebo challenge in endogenous depression. Psychiatr Res 43:137–146.

Lindvall O, Bjorklund A. 1984. General organization of cortical monoamine systems. In: Descarries L, Reader T, Jasper H, editors. Monoamine innervation of cerebral cortex. New York: Alan R. Liss, Inc. p 9–40.

Maas J, Fawcett J, Dekirmenjian H. 1972. Catecholamine metabolism, depressive illness and drug response. Arch Gen Psychiatry 26:252–262.

Maes M, Jacobs MP, Suy E, Minner B, Leclercq C, Christiaens F, Raus J. 1990. Suppressant effects of dexamethasone on the availability of plasma L-tryptophan and tyrosin in healthy controls and in depressed patients. Acta Psychiatr Scand 81:19–23.

Maes M, Meltzer H. 1995. The serotonin hypothesis of major depression. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 933–944.

Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N, Baldwin RM, Seibyl JP, Innis RB, Charney DS. 1998. Reduced brain serotonin transporter availability in major depression as measured by [^{123}I]-2 β-carbomethoxy-3 β-(4-iodophenyl) tropane and single photon emission computed tomography. Biol Psychiatry 44:1090–1098.

Mamounas L, Blue M, Siuciak J, Anthony A. 1995. BDNF promotes the survival and sprouting of serotonergic axons in the rat brain. J Neurosci 15:7929–7939.

Mann J, Stanley M, McBride P, McEwen BS. 1986. Increased 5HT$_2$ and β-adrenergic receptor binding in the frontal cortices of suicide victims. Arch Gen Psychiatry 43:954–959.

Mann JJ, McBride PA, Malone KM, DeMeo M, Keilp J. 1995. Blunted serotonergic responsivity in depressed patients. Neuropsychopharmacology 13:53–64.

Mann J, Underwood M, Arango V. 1996. Postmortem studies of suicide victims. In: Watson S, editor. Biology of schizophrenia and affective disease. Washington, DC: American Psychiatric Press, Inc. p 197–222.

Mann J. 1999. Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. Neuropsychopharmacology 21:99S–105S.

Mansour A, Meador-Woodruff J, Lopez J, Watson S. 1998. Biochemical anatomy: insights into the cell biology and pharmacology of the dopamine and serotonin systems in the brain. In: Schatzberg A, Nemeroff C, editors. Textbook of psychopharmacology, 2nd ed. Washington: American Psychiatric Press. p 55–74.

Mattsubara S, Arora R, Meltzer H. 1991. Serotonergic measures in suicide brain: 5-HT$_{1a}$ binding sites in frontal cortex of suicide victims. J Neural Transm 85:181–194.

Matussek N, Ackenheil M, Hippius H, Muller F, Schroder HT, Schultes H, Wasilewski. 1980. Effects of clonidine on growth hormone release in psychiatric patients and controls. Psychiatry Res 2:25–36.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 156:675–682.

McDonald A. 1998. Cortical pathways to the mammalian amygdala. Prog Neurobiol 55:257–332.

McEwen B. 1999. Stress and hippocampal plasticity. Annu Rev Neurosci 22:105–122.

Meana J, Barturen F, Garcia-Sevilla J. 1992. α_2-Adrenoceptors in the brains of suicide victims: increased receptor density associated with major depression. Biol Psychiatry 31:471–490.

Melia K, Rasmussen K, Terwilliger R, Haycock JW, Nestler EJ, Duman RS. 1992. Coordinate regulation of the cyclic AMP system with firing rate and expression of tyrosine hydroxylase in the rat locus coeruleus: effects of chronic stress and drug treatments. J Neurochem 58:494–502.

Mongeau R, Blier P, de Montigny C. 1997. The serotonergic and noradrenergic systems of the hippocampus: their interactions and the effects of antidepressant treatments. Brain Res Rev 23:145–195.

Morgan M, Romanski L, LeDoux J. 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett 163:109–113.

Morgan M, LeDoux J. 1995. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behav Neurosci 109:681–688.

Nemeroff C, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W. 1984. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 226:1342–1344.

Nemeroff C, Knight D, Krishnan K, et al. 1988. Marked reduction in the number of platelet [^{3}H]imipramine binding sites in geriatric depression. Arch Gen Psychiatry 45:919–923.

Nemeroff C. 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol Psychiatry 1:336–342.

Nemeroff C. 1998. Psychopharmacology of affective disorders in the 21st century. Biol Psychiatry 44:517–525.

Nestler E, McMahon A, Sabban E, Tallman JF, Duman RS. 1990. Chronic antidepressant administration decreases the expression of tyrosine hydroxylase in the rat locus coeruleus. Proc Natl Acad Sci USA 87:7522–7526.

Ninan P. 1999. The functional anatomy, neurochemistry, and pharmacology of anxiety. J Clin Psychiatry 60(Suppl):12–17.

O'Keane V, McLoughlin D, Dinan T. 1992. D-fenfluramine-induced prolactin and cortisol release in major depression: response to treatment. J Affect Disord 26:143–150.

Olivier B, van Oorschot R, Waldinger M. 1998. Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behavior. Int Clin Psychopharmacol 13:S9–S14.

Ongur D, Drevets W, Price J. 1998. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci 95:13290–13295.

Ordway G, Smith K, Haycock J. 1994a. Elevated tyrosine hydroxylase in the locus coeruleus of suicide victims. J Neurochem 62:680–685.

Ordway G, Widowson P, Smith K, Halaris A. 1994b. Agonist bind-

ing to α_2 adrenoceptors is elevated in the locus coeruleus from victims of suicide. J Neurochem 63:617–624.

Owens MJ, Bartolome J, Schanberg SM , Nemeroff CB. 1990. Corticotropin-releasing factor concentrations exhibit an apparent diurnal rhythm in hypothalamic and extrahypothalamic brain regions: differential sensitivity to corticosterone. Neuroendocrinology 52:626–631.

Owens MJ, Nemeroff CB. 1994. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem 40:288–295.

Owens MJ. 1997. Molecular and cellular mechanisms of antidepressant drugs. Depress Anxiety 4:153–159.

Papadopoulos G, Parnavelas J, Buijs R. 1990. Monoaminergic fibers form conventional synapses in the cerebral cortex. Neurosci Lett 76:275–279.

Pineyro G, Blier P, Dennis T, deMontigny C. 1994. Desensitization of the neuronal 5HT carrier following its long-term blockade. J Neurosci 14:3036–3047.

Plotsky P, Owens M, Nemeroff C. 1998. Psychoneuroendocrinology of depression. Psychiatr Clin North Am 21:293–307.

Potter W, Muscettola G, Goodwin F. 1983. Sources of variance in clinical studies in MHPG. In: Maas J, editor. MHPG: basic mechanisms and psychopathology. New York: Academic Press. p 145–165.

Potter WZ, Scheinin M, Golden RN, Rudorfer MV, Cowdry RW, Calil HM, Ross RJ, Linnoila M. 1985. Selective antidepressant and cerebrospinal fluid: lack of specificity on noradrenaline and serotonin metabolism. Arch Gen Psychiatry 42: 1171–1177.

Potter W, Grossman G, Rudorfer M. 1993. Noradrenergic function in depressive disorders. In: Mann J, Jupter D, editors. Biology of depressive disorders. Part A: a systems perspective. New York: Plenum Press. p 1–27.

Price J, Charmichael S, Drevets W. 1996. Networks related to the orbital and medial prefrontal cortex: a substrate for emotional behavior? Prog Brain Res 107:523–536.

Price LH, CHarney DS, Delgado PL, Heninger GR. 1991. Serotonin function and depression. Neuroendocrine and mood responses to intravenous L-tryptophan in depressed patients and healthy comparison subjects. Am J Psychiatry 148:1518–1525.

Raadsheer F, Hoogendijk J, Stam F, Tilders FJ, Swaab DF. 1994. Increased number of corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology 60:436–444.

Raadsheer F, van Heerikhuize J, Lucassen PJ, Hoogendijk WJ, Tilders FJ, Swaab DF. 1995. Corticotropin-releasing hormone (CRH) mRNA in paraventricular nucleus of patients with Alzheimer disease or depression. Am J Psychiatry 152:1372–1376.

Rainnie D. 1999. Serotonergic modulation of neurotransmission in the rat basolateral amygdala. J Neurophysiol 82:69–85.

Rajkowska G, Miguel-Hidalgo J, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA. 1999. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 45:1085–1098.

Rauch S, Jenicke M, Alpert N, Baer L, Breiter HC, Savage CR, Fischman AJ. 1994. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch Gen Psychiatry 51:62–70.

Ressler K, Nemeroff C. 1999. Role of norepinephrine in the pathophysiology and treatment of mood disorders. Biol Psychiatry 46:1219–1233.

Robbins T, Everitt B. 1995. Central norepinephrine neurons and behavior. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 363–372.

Roy A, Jimerson D, Pickar D. 1986. Plasma MHPG in depressive disorders and relationship to the dexamethasone suppression test. Am J Psychiatry 126:457–469.

Roy A, Pickar D, DeJong D, Karoum F, Linnoila M. 1988. Norepinephrine and its metabolites in cerebrospinal fluid, plasma and urine: relationship to hypothalamic-pituitary-adrenal axis function in depression. Arch Gen Psychiatry 45:849–857.

Roy A, DeJong J, Linnoila M. 1989. Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients. Arch Gen Psychiatry 46:609–612.

Schatzberg A, Schildkraut J. 1995. Recent studies on norepinephrine systems in mood disorders. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 911–920.

Schildkraut J. 1965. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 122:509–522.

Segal M. 1990. Serotonin attenuates a slow inhibitory postsynaptic potential in rat hippocampal neurons. Neuroscience 36:631–641.

Sevy S, Papadimitriou G, Surmount D, et al. 1989. Noradrenergic function in generalized anxiety disorder, major depressive disorder, and healthy subjects. Biol Psychiatry 25:141–152.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. 1996. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci 93:3908–3913.

Siever L, Trestman R, Coccaro E. 1992. The growth hormone response to clonidine in acute and remitted depressed male patients. Neuropsychopharmacology 6:165–177.

Smith H, Daunais J, Nader M, Porrino L. 1999. Distribution of [^{3}H] citalopram binding sites in the nonhuman primate brain. Ann NY Acad Sci 877:700–702.

Stanford S, Nutt D. 1982. Comparison of the effects of repeated electroconvulsive shock on α_2 and β-adrenoceptors in different regions of rat brain. Neuroscience 7:1753–1757.

Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B, Mann JJ. 2000. Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. Am J Psychiatry 157:609–614.

Stutzmann G, McEwen B, LeDoux J. 1998. Serotonin modulation of sensory inputs to the lateral amygdala: dependency on corticosterone. J Neurosci 18:9529–9538.

Sullivan GM, Coplan JD, Kent JM, Gorman JM. 1999. The noradrenergic system in pathological anxiety: a focus on panic with relevance to generalized anxiety and phobias. Biol Psych 46: 1205–1218.

Svensson T. 1980. Effect of chronic treatment with tricyclic antidepressant drugs on identified brain noradrenergic and serotonergic neurons. Acta Psychiatr Scand 61:121–131.

Tiller J, Biddle N, Maguire K, Davies BM. 1988. The dexamethasone suppression test and plasma dexamethasone in generalized anxiety disorder. Biol Psychiatry 23:261–270.

Tork I. 1990. Anatomy of the serotonergic system. Ann NY Acad Sci 600:9–35.

Valentino R, Foote S, Page M. 1993. The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. Ann NY Acad Sci 697:171–187.

Valentino R, Aston-Jones G. 1995. Physiological and anatomical determinants of locus coeruleus discharge. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd. p 373–385.

Van Bockstaele E, Peoples J, Valentino R. 1999. Anatomic basis for differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. Biol Psychiatry 46:1352–1363.

Vetulani J, Sulser F. 1975. Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generation system in limbic forebrain. Nature 257:495–496.

Waterhouse BD, Sessler FM, Cheng JT, Woodward DJ, Azizi SA, Moises HC. 1988. New evidence for a gating action of norepinephrine in central neuronal circuits of mammalian brain. Brain Res Bull 21:425–432.

Weiner N, Molinoff P. 1994. Catecholamines. In: Siegel G, Agranoff B, Albers R, Molinoff P, editors. Basic neurochemistry: molecular, cellular, and medical aspects, 5th edition. New York: Raven Press, Ltd. p 261–281.

Weiss JM, Stout JC, Aaron MF, Quan N, Owens MJ, Butler PD, Nemeroff CB. 1994. Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. Brain Res Bull 35:561–572.

Wyatt R, Portnoy B, Kupfer D, Snyder F, Engelman K. 1971. Resting plasma catecholamine concentrations in patients with depression and anxiety. Arch Gen Psychiatry 24:65–70.

Zhuang X, Gross C, Santarelli L, Compan V, Trillat AC, Hen R. 1999. Altered emotional states in knockout mice lacking 5-HT_{1a} or 5-HT_{1b} receptors. Neuropsychopharmacology 21: 52S–60S.