

Overview

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

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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 noreadrenergic 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 pharmaco-economic 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.

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Research Reviews

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

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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.

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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

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[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 char-

acterized 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 (β AR), α_1 adrenergic, and α_2 adrenergic receptors. β AR is the principle postsynaptic receptor and is excitatory on the postsynaptic membrane. At least three different subtypes of β AR exist (β AR₁₋₃), 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 5HT₁ class are located both pre- and postsynaptically, and is inhibitory through reduction of adenylate cyclase activity via G_i activation. The 5HT₂ class is predominantly postsynaptic, and excitatory through activation of phospholipase C via G_q. The 5HT₄, 5HT₅, and 5HT₆ classes all activate adenylate cyclase via G_s. In contrast, the 5HT₃ 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 5HT₂ 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 heteroreceptors. Thus inhibitory α_2 receptors have been localized on 5HT terminals and excitatory 5HT₃ re-

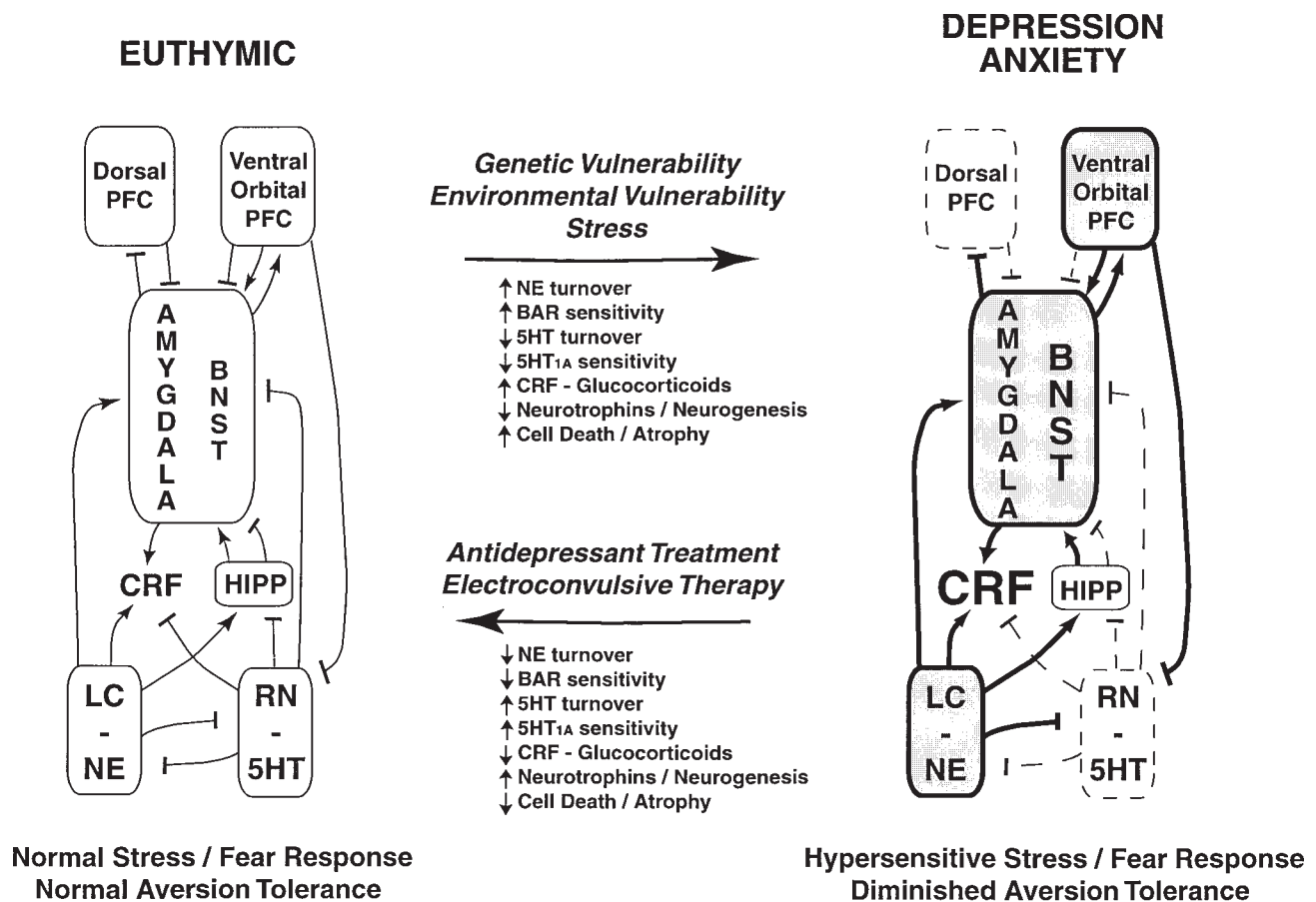


Figure 1. The brainstem modulatory nuclei, locus coeruleus with norepinephrine (LC-NE) and raphe nuclei with serotonin (RN-5HT), are shown with their primary excitatory (→) and inhibitory (—) effects on limbic circuitry. The limbic system modulates affective state and approach/avoidance behavior, states 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 lo-

cal NE release mediated by the 5HT₃ receptor, that may subsequently decrease or tonically inhibit 5HT release via NE activation of the presynaptic α₂ 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 5HT₂ 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 5HT₂ 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 (*vide 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 β AR desensitization all result in a net increase in 5HT_{1A} post-synaptic transmission and a net decrease in β AR 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]. Monoamines 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 ambiguus/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 Benfield, 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]. Anti-depressant 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 stress-

ful/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.

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