73

NEUROCIRCUITRY OF MOOD DISORDERS

GREGORY A. ORDWAY
VIOLETTA KLIMEK
J. JOHN MANN

One of the first neurochemical theories of depression was the monoamine deficiency hypothesis (139,143,153). Over the past 30 years, this hypothesis has been the most scrutinized of any theories regarding the biology of depression. Unfortunately, the biology of depression remains an elusive issue, despite intense biological research. It is widely held that most, if not all, antidepressant drug treatments produce their therapeutic antidepressant effects, at least in part, by modulating monoamine systems (noradrenergic, serotonergic, and dopaminergic); however, less is known about the neurochemical pathology of these monoamine systems in depression. Early attempts to evaluate monoamine systems in depressive disorders led to diverse and not clearly integrated findings. As a result, many other neurochemical theories have been generated in efforts to explain the biological basis of depression. These theories include HPA axis hyperactivity (111), the GABA hypothesis (132), the galanin hypothesis (186), the substance P hypothesis (82), the glutamate hypothesis (162), the neurotrophin hypothesis (39), and many others. A substantial portion of the evidence supporting these ''other neurotransmitter'' theories derives from studies of the pharmacologic and behavioral effects of antidepressant drugs in laboratory animals. Of course, these antidepressant drugs have prominent actions on norepinephrine (NE), serotonin (5HT), and to a lesser extent, dopamine (DA). Hence, originators of new hypotheses are continuously forced to place new theories in the context of the old monoamines. The principal reason for this is that, despite years of pharmaceutical development, drugs with primary actions on monoamine systems remain the mainstay of treatment for depressive disorders. In fact, evidence that there has been an improvement of medication over the past 20 years is highly debated, in terms of greater efficacy or even faster onset of action. If improvements are evident in antidepressant medications, then they are as a result of a reduction of adverse side effects with newer antidepressant compounds, rather than novel pharmacologic mechanisms with enhanced activity. For this reason, as research on depression biology progresses into this new century, the monoamine hypotheses continue to be among the most popular biological theories and continue to be heavily investigated and debated.

Much of the past 10 years of research in the biology of mood disorders has led to advancements in our understanding of the role that monoamines play in these disorders. New modern approaches have been applied, including the use of *in vivo* imaging techniques in live patients, morphologic and neurochemical investigations with high levels of anatomic resolution, use of postmortem brain tissues from psychiatrically characterized subjects, and genetic studies. Considerable evidence has accumulated implicating multiple system pathology in mood disorders, including abnormalities of monoamine as well as other neurotransmitter systems. These approaches and findings have led researchers to propose broader theories regarding depression biology (e.g., depression as a spreading neuronal adjustment disorder or limbic–cortical dysregulation disorder) (67,102). In this chapter, the authors reconcile new findings of multiple system pathologies specifically with regard to monoaminergic systems. Emphasis is placed on the cellular sources of monoamine systems and their circuitry, the communication between these monoamine nuclei, and the influence of other neurotransmitter systems that are putatively disrupted in depression on monoaminergic neuronal activity.

NORADRENERGIC CIRCUITRY AND DEPRESSION

The original speculation that NE is deficient in depression hinged partly on clinical observations of depression in some

Gregory A. Ordway and Violetta Klimek: Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, Mississippi.

J. John Mann: Department of Neuroscience, New York State Psychiatric Institute, New York, New York.

individuals receiving reserpine for hypertension. Reserpine depletes brain monoamines by blocking vesicular monoamine storage; however, only a fraction of individuals administered reserpine develops depression. In fact, short-term depletion of NE by administration of alpha-methyl-*p*-tyrosine to normal control subjects does not result in a significant change in mood (152). These findings, along with a history of inconsistent findings regarding levels of NE and its metabolites in depressive disorders (19,138,147,180), casted doubt about NE's role in depression for many years. Recently, however, Charney and co-workers (28) demonstrated that rapid pharmacologic depletion of NE in patients taking noradrenergic antidepressants causes a rapid relapse of depression. This latter finding demonstrates that NE is critical to the therapeutic action of noradrenergic antidepressant drugs. Most recently, and of considerable significance, is the demonstration that depletion of catecholamines (NE and DA) in unmedicated fully remitted subjects with histories of major depression resulted in relapse into depression (21). Together, these studies demonstrate that acute NE depletion is insufficient to induce depressive symptoms by itself, but depletion in a susceptible individual induces depressive symptoms.

The neurobiological relationship between NE and mood is poorly understood. Most of the NE in the brain arises from cell bodies in the locus ceruleus (LC). The projections of these neurons are diffuse and overlapping with respect to the brain regions innervated. Some of the brain regions that are most densely innervated by the LC are limbic brain regions, including the amygdala and hippocampus. The LC is part of the reticular activating system and neurons of the LC have tonic pacemaker activity. LC activity is elevated during states of arousal. In contrast, LC activity slows during sleep and is inactive during random eye movement (REM) sleep. The LC is robustly activated by stress, contributing to the alerting of the organism to stimuli relevant to survival. In addition to innervation of forebrain regions, the LC densely innervates other monoaminergic nuclei, including the serotonergic raphe nuclei and the dopaminergic ventral tegmental area (VTA) (10,116). Given the large number of brain regions innervated by the LC, noradrenergic transmission is in an ideal position to globally modulate brain function, and modulate the activity of other monoamines. Foote and colleagues (51) and Aston-Jones and associates (10) have extensively reviewed the physiologic consequences of LC activation.

The hypothesis that NE plays a role in the neurochemical pathology of depression raises the possibility that the activity and biochemistry of the noradrenergic LC is abnormal in this illness. Recent studies using postmortem brain tissues from psychiatrically characterized subjects reveal a complex pathology of the noradrenergic LC in major depression. These studies are unique with respect to many previous postmortem research studies on the noradrenergic system in depression because of the focus on neurons that are the source of NE and because brain tissues utilized were from subjects whose psychiatric status was rigorously characterized (80,195). Prominent among exclusion criteria for subjects is the absence of any antidepressant (or antipsychotic) drug use, determined both by next-of-kin interview and from a toxicology examination. Elevated amounts of tyrosine hydroxylase (TH) (195) elevated binding to α_2-adrenoceptors (119,122) and reduced amounts of NE transporter binding (80) have been reported in the LC of major depressive subjects as compared to psychiatrically normal control subjects. In contrast, other proteins measured in the LC of major depressives appear to occur in normal amounts (e.g., monoamine oxidase A, MAO-A) (118). Interestingly, a lower number of noradrenergic neurons have been observed in the rostral LC from victims of suicide relative to normal control subjects (5). In contrast, Klimek and co-workers (80,195) report no differences in noradrenergic neuron cell counts in the middle to caudal portion of the LC between depressed suicide victims and psychiatrically normal control subjects, or in psychiatrically uncharacterized suicide victims compared to control subjects (120). Elevation of radioligand binding to some (3), but not all, noradrenergic receptors (4,79) has also been identified in some projection areas of the LC, comparing suicide victims to control subjects.

To interpret these postmortem findings, it is very useful, if not necessary, to utilize information from studies of NE in laboratory animals. In animals, stress activates the LC (130) and exposure to repeated stress elevates the demand for NE (110,124) revealed by increases in LC TH (105,175, 183). Uncontrollable shock, a stress-based animal model of depression, increases the release of NE (187) and reduces NE stores (187). Because TH is the enzyme catalyzing the rate-limiting step in the synthesis of NE, increased tyrosine hydroxylase in the LC may adjust the set point of basal activity in the NE system, to keep pace with increased demand. Similar examples of up-regulation of TH expression in the LC occur after administration of reserpine (31) and intraventricular infusion of 6-hydroxydopamine (106), both of which cause loss of brain NE. Pharmacologic depletion of NE also up-regulates binding to α_2-adrenoceptors (60,172) and down-regulates binding to NE transporter (86). Hence, postmortem findings of LC biochemistry (e.g., elevated tyrosine hydroxylase and α_2-adrenoceptor binding) and reduced NE transporter binding are predictive of premortem increases in LC activity and decreases of NE availability. Decreased NE availability could also contribute to compensatory up-regulation of β-adrenoceptors in LC projection areas, such as has been observed in the frontal cortex from suicide victims (3). As mentioned, the link between reduced brain NE and depressive symptoms, at least in susceptible individuals, has been made (21). Moreover, the relevance of stress-induced biochemical abnormalities in the LC is underscored by studies demonstrating a relationship between life stress and development of depression (26), and

that stress plays a role in the etiology of depression (131). A shortcoming of the cited postmortem studies, however, is that most of the depressive subjects who have been studied died as a result of suicide, and the relationship between the biological abnormalities found in the central noradrenergic system and behaviors related to suicide that are distinct from those related to depression has not been investigated.

If one accepts that biological abnormalities in the noradrenergic LC are relevant to the symptoms of depression, then it follows that treatment with antidepressant drugs might reverse these abnormalities. Again, it is presently necessary to look to laboratory animal studies to examine this issue. Repeated treatment of rats with antidepressants from many different pharmacologic classes (including 5HT uptake inhibitors), but not with non-antidepressant drugs, down-regulates LC tyrosine hydroxylase (114). Antidepressant drug treatment blocks stress-induced elevation of tyrosine hydroxylase mRNA in the rat LC (154). Repeated antidepressant drug treatment also down-regulates α_2-adrenoceptors in the rat LC (154). These findings demonstrate that repeated antidepressant treatment down-regulates tyrosine hydroxylase and α_2-adrenoceptors, proteins that are apparently up-regulated in the LC of human major depressives. Returning to the suggestion that LC activity may be elevated in depressives, recent studies demonstrate that repeated treatment of rats with antidepressant drugs of many different pharmacologic classes (including 5HT uptake inhibitors) reduces LC activity (58,68). Hence, animal data strongly support the contention that drugs produce antidepressant effects, at least in part, by reducing demand for NE, that is, reducing biochemical measures of demand (reduced biosynthetic enzyme for NE) and reducing LC activity.

In summary, evidence of: 1) norepinephrine depletion-induced depression in susceptible human subjects, 2) abnormal levels of noradrenergic proteins in the LC of human major depressives, 3) the ability of antidepressant medication to produce effects that would be expected to reverse noradrenergic pathology in depression provide strong support for the venerable theory that norepinephrine plays a role in the pathobiology of depression.

SEROTONERGIC CIRCUITRY AND DEPRESSION

The biological basis for the indoleamine hypothesis was similar to that for the catecholamine hypothesis (178). That is, reserpine depletes not only catecholamines, but also 5HT. Since that time, several (but not all) studies have found reduced levels of CSF 5-hydroxyindole acetic acid (5-HIAA) in depressed patients (101,179); however, the degree of reduction of CSF 5-HIAA does not correlate with severity of depression. Oddly, many antidepressant medications, particularly 5HT reuptake inhibitors and monoamine oxidase inhibitors (MAOIs), reduce CSF 5-HIAA, possibly because of feedback inhibition resulting from increased synaptic concentrations of 5HT. Levels of CSF 5-HIAA are lower in depressed patients with a history of serious suicidal behavior, as compared to depressed patients with no history of suicide attempts. (See ref. 99 for review.) CSF 5-HIAA levels appear to exhibit a bimodal distribution in depressed patients. CSF 5-HIAA is not distinguished by more severe depression, but by a history of serious suicide attempts (55). Rapid tryptophan depletion causes transient, mild, nonclinical increases in negative mood in healthy young men (36). In depressed patients who had recent therapeutic responses to antidepressant medications, tryptophan depletion causes a transient depressive relapse (35). Rapid tryptophan depletion of many, but not all, patients with a history of depression and that are antidepressant drug-free causes a depressive relapse (35,164). In symptomatic, medication-free patients with depression, tryptophan depletion causes no significant behavioral effects (36), perhaps because of a floor effect (36). Together, these findings suggest that depression is often, but not always, associated with a serotonergic deficit.

A number of neuroendocrine challenge tests have demonstrated impaired serotonergic activity in depressed patients (49,56,69), although conflicting findings have also been reported. (See ref. 98 for review.) Numerous researchers have utilized postmortem brain tissues to study the serotonergic system in depression. Measurement of both $5HT_{1A}$ and $5HT_{2A}$ receptors in the prefrontal cortex from suicide victims has yielded no clear conclusions. Most of the studies cited in a recent review of these data by Stockmeier and colleagues (165) utilized tissues primarily from victims of suicide. Because there is an association of serotonergic abnormalities with suicidal risk, it is difficult to determine what effects are attributable to the presence of major depression from those associated with suicidal behavior (98). Significant increases in $5HT_{2A}$ receptor binding and a decrease in 5-HIAA in major depressives dying of causes other than suicide have been reported (47,103).

Given substantial evidence that 5HT plays a role in the pathology of major depression, it is expected that neurons supplying affected areas of the brain would display neuronal or neurochemical pathology. Two major nuclei in the brain, from which the majority of brain serotonergic innervation originates, are the dorsal raphe and median raphe nuclei. These nuclei provide an extensive innervation of cortical and subcortical target areas. The dorsal and median raphe nuclei give rise to separate axonal pathways to different brain regions. For example, the septum and hippocampus are innervated predominantly by the median raphe nuclei. In contrast, the striatum and substantia nigra are innervated by the dorsal raphe nuclei. Serotonergic terminals densely innervate various components of the limbic system. The widespread innervation of the brain by serotonergic neurons is the anatomic basis for the influence of 5HT on many diverse brain functions.

Several recent studies have investigated the serotonergic raphe in depression. Using single photon emission computed tomography (SPECT), Malison and associates (97) reported a decrease in 5HT transporter availability in the brainstem of living subjects with major depression. Because of issues related to spatial resolution, it is difficult to conclude from this study that the reduction in 5HT transporter occurred in raphe nuclei and/or other brainstem nuclei where the 5HT transporter occurs (e.g., substantia nigra or VTA). Little and co-workers (90) found no significant change in mRNA for the 5HT transporter in the dorsal raphe and median raphe nuclei from depressed persons who had committed suicide. Consistent with these findings, Bligh-Glover and colleagues (25) found no significant differences between depressed suicide victims and normal control subjects in [^{3}H]paroxetine binding to the 5HT transporter in the entire dorsal raphe or in its constituent subnuclei, as determined using postmortem tissues from psychiatrically characterized subjects. An increase in radioligand binding to $5HT_{1A}$ autoreceptors in dorsal raphe nuclei from depressed suicide victims has been observed (166). In apparent contrast, a decrease in the binding potential to $5HT_{1A}$ receptors in the midbrain raphe nuclei has been observed using positron emission tomography (PET) in patients with familial mood disorder (38). Recent studies also provide evidence of morphologic abnormalities of brainstem serotonergic nuclei. Underwood and associates (173) have demonstrated elevated numbers and densities of 5HT neurons in the dorsal raphe of suicide victims, most of whom had major depression. In addition, Becker and colleagues (18) have demonstrated significantly low echogenicity of the dorsal raphe nucleus in patients with major depression using a novel transcranial ultrasound technique. Together, these findings are strongly suggestive of a neuropathologic involvement of brainstem serotonergic nuclei in depression, but the study by Underwood and associates ruled out a loss of serotonergic neurons in depressed suicides, suggesting that the postulated hypofunction of the serotonergic system is not owing to fewer serotonergic neurons, but dysfunction of serotonergic neurons. As is the case with noradrenergic pathology, the specificity of serotonergic pathology for major depression versus suicidal behavior is yet to be clarified.

Evidence of a serotonergic deficit in depression predicts that drugs that are effective antidepressants should enhance serotonergic transmission. In fact, repeated treatment of rats with antidepressant drugs results in a net enhancement of serotonergic transmission (24). This effect is regardless of the primary pharmacologic site of action of the drug and includes selective 5HT transporter inhibitors, MAOIs, tricyclic antidepressants, and electroconvulsive shock. Selective 5HT transporter inhibitors and MAOIs enhance serotonergic transmission by desensitizing the somatodendritic $5HT_{1A}$ autoreceptors (23,24) and enhancing responsiveness of postsynaptic $5HT_{1A}$ receptors (63). Chronic administration of some tricyclic antidepressants or a course of electroconvulsive shock to rats does not appear to desensitize somatodendritic autoreceptors, although these treatments enhance the responsiveness of postsynaptic 5HT receptors (24,107). Hence, the mechanism by which different antidepressant drugs regulate serotonergic activity appears to differ, but the net effect of enhancing serotonergic transmission is similar. These preclinical findings are consistent with the hypothesis that there is a deficit in serotonergic transmission in depressive disorders that is normalized or corrected by antidepressant drug administration.

DOPAMINERGIC CIRCUITRY AND DEPRESSION

Since the discovery that tricyclic antidepressant drugs can block DA reuptake *in vitro* (66), and that elevation of the functional activity of DA has antidepressant efficacy (142, 143), there has been interest in the potential role of DA in the pathophysiology of depression. The contribution of DA to emotion-laden behaviors such as reward seeking, motivation, and environmental responsiveness also raises speculation that DA plays a role in the pathobiology of depression (48,167). In fact, clinical, pharmacologic, and laboratory animal evidence suggests that dopaminergic neurotransmission is decreased in depression. Lower concentrations of homovanillic acid (HVA), a DA metabolite, have been observed in CSF of patients with depression, and depression-inducing effects of DA-depleting agents or DA antagonists have been reported (143,144,189). In contrast, agents that enhance DA transmission, at least in part, such as bupropion, nomifensine, and amineptine, exert antidepressant effects in humans. Given that DA is intimately involved in motivational process and affect (73,167), these findings suggest that a deficiency of mesolimbic and/or mesocortical DA is a leading candidate for the etiology of core symptoms of depression, such as difficulty in the experience of pleasure (anhedonia), social isolation, loss of motivation (lack of interest), and psychomotor retardation (190).

At least three DA systems putatively involved in neurologic and psychiatric disorders have been extensively characterized in the brain: the nigrostriatal, mesolimbic, and mesocortical systems. A loss of nigrostriatal DA neurons causes the motor impairment of Parkinson's disease (PD), whereas dysfunction or activation of mesolimbic and/or mesocortical DA systems are implicated in psychiatric disorders, including depression, schizophrenia, and psychostimulant drug abuse disorders. However, some overlap in the pathology of PD and psychiatric disorders apparently occurs because cell loss in the VTA (in addition to substantia nigra) has been observed in patients with PD who have complications of co-morbid mood and cognitive disorders (171).

Anatomic, electrophysiologic, and neurochemical studies have delineated reciprocal pathways linking various limbic

and cortical regions with dopaminergic brainstem nuclei. Kalivas and Nakamura described the neuronal circuit that mediates the integration of reward perception and adaptive behavioral responses (75). This circuit includes the nucleus accumbens, amygdala, prefrontal cortex, mediodorsal thalamus, ventral pallidum, and midbrain neurons located in the VTA. Of brain limbic structures, the nucleus accumbens (ventral striatum) has been considered an important anatomic substrate of psychiatric illness, because of its established role in motivation and affect (167,75). Neurons in the nucleus accumbens receive a highly compressed input from the amygdala, hippocampus, cingulate gyrus, and prefrontal cortex (68,194). Ascending to synapse onto the same neurons in the nucleus accumbens are DA-containing fibers from the VTA (68), suggesting that the nucleus accumbens may integrate information coming from the prefrontal cortex and limbic regions with those originating from the VTA. Besides projecting to the nucleus accumbens, DA neurons ascending from the VTA project to other limbic structures, including discrete regions of amygdala, to cortical areas, and to the septum (116). Prefrontal, orbitofrontal, and cingulate cortices receive robust innervation from the VTA. Interestingly, most of the areas receiving DA projections from the VTA project back to the VTA.

If DA neurotransmission were disrupted in depression, then antidepressant drug treatment would be expected to produce effects on the brain dopaminergic system. Numerous studies demonstrate that antidepressant drugs enhance mesolimbic DA activity. Repeated treatment of rats with antidepressant drugs (tricyclics, mianserin, or citalopram) enhances DA agonist-induced locomotor hyperactivity, an effect observed when DA agonists are administered either systemically or injected directly into the nucleus accumbens (94–96). It is noteworthy that stereotypy (a behavioral effect reflecting the activity of nigrostriatal system) induced by D-amphetamine or apomorphine, is not increased by repeated treatment with antidepressant drugs (156); therefore, it has been assumed that the mesolimbic DA system mediates the increased behavioral responses to DA agonists following antidepressant treatments. Consistent with this effect, antidepressant drug treatment increases the affinity of D_2 receptors for their agonist in the limbic forebrain, but not in the striatum (78) and chronic treatment with antidepressant drugs results in postsynaptic DA receptor supersensitivity in the nucleus accumbens (40). Recent autoradiography studies confirm these findings by showing that when [^{3}H]raclopride, an antagonist at $D_{2/3}$ receptors, is used as a radioligand, no significant differences in the density of $D_{2/3}$ receptors are observed after chronic antidepressant drug administration. In marked contrast, when [^{3}H]quinpirole, an agonist at $D_{2/3}$ receptors is used as a radioligand, a significant increase in its binding is observed in the caudate and NAC of antidepressant-treated rats (146).

The level of mRNA encoding the D_1 receptor and [^{3}H]SCH 23390 binding to D_1 receptors are decreased in the limbic regions following these antidepressant drug treatments (42,37). A lower density of D_1 receptors induced by chronic antidepressant medication might contribute to enhancement of D_2 receptor functions as a result of a reduction in the inhibitory interactions between these two receptors at the level of the $\beta\gamma$ subunit of G proteins (182).

Behavioral models in laboratory animals also point to a role for DA in antidepressant drug action. Following exposure to uncontrollable foot shock, an animal model of depression, rats display a pronounced reduction of responding for electrical brain stimulation of the nucleus accumbens. This response is attenuated by repeated treatment with the antidepressant drug desipramine (193). Rats exposed to chronic mild stress, another animal model of depression, experience decreased responsiveness to rewards (anhedonia), which is antidepressant-reversible (191). These behavioral changes are accompanied by lower $D_{2/3}$ receptor binding in the limbic forebrain that is reversed by 5 weeks of imipramine treatment (127). Overall, preclinical findings imply that a putatively important pharmacologic effect of antidepressant treatment is the augmentation of mesolimbic DA activity.

A few recent studies have measured the DA receptors in depressed patients *in vivo* using brain imaging techniques. Two studies demonstrate an increase of D_2 receptor density in the striatum in depression, possibly reflecting reduced DA function and a consequential up-regulation of these receptors (33,157). On the other hand, Ebert and associates, 1996 (43) found striatal D_2 receptor binding unchanged in major depression.

INTERACTIONS BETWEEN THE MONOAMINE NUCLEI AND MONOAMINES AND OTHER NEUROTRANSMITTERS

Abnormalities of the biochemistry of one or more monoamine systems may cause depressive disorders. Alternatively, disrupted monoamine biochemistry may be secondary to other root biological, environmental, and/or psychological causes. A multitude of experimental approaches will be required to determine the core cause(s) of depressive disorders, even as considerable evidence of monoamine dysfunction in depression accumulates. Nevertheless, it is interesting to consider the relationship of the monoamines with other neurotransmitters that modulate monoaminergic chemistry. The LC, raphe nuclei and VTA receive a variety of neuronal inputs, including the monoamines themselves, that regulate their activity (Fig. 73.1). Several neurotransmitter inputs to monoamine nuclei are of particular relevance to major depression because of the accumulation of evidence that these systems are also disrupted in depression. For example, abnormalities in GABA, substance P, corticotropin releasing factor (CRF) and glutamate neurochemistry have been im-

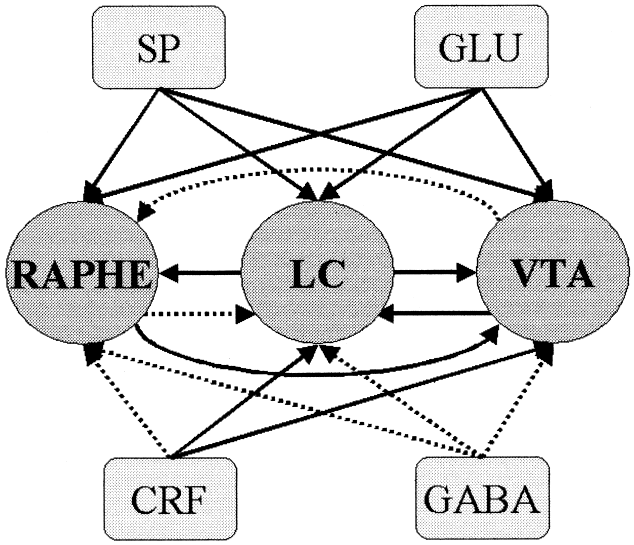

FIGURE 73.1. Neurotransmitter interactions at the level of monoaminergic cell bodies. Solid lines represent excitatory inputs to the raphe nuclei, LC, and VTA; dashed lines represent inhibitory inputs. In some cases, neurotransmitter inputs may be both direct and indirect via synapses with other neurons projecting to the nuclei. Neurotransmitters inputs shown are only those that are discussed in this chapter.

plicated in depression. Theoretically, disruption of the activity of monoamine systems could result from disease-related abnormalities in neurotransmitter input to the monoamine nuclei. In addition, disruption of serotonergic activity in depression could be secondary to deficient noradrenergic input to the serotonergic raphe nuclei. That is, disruption of one monoamine would be expected to result in general monoamine imbalance because of the inter-connectivity between these nuclei. Hence, the relationship between the monoamine systems, and between monoamines and other neurotransmitter systems suspected of playing a role in depression biology, is worthy of discussion.

Monoamine Interactions at the Level of the Monoaminergic Nuclei

The monoaminergic nuclei are highly interconnected and physiologically integrated. For example, noradrenergic neurons innervate the serotonergic raphe nuclei and the dopaminergic VTA. Both the dorsal and median raphe nuclei receive noradrenergic innervation (15,121). In fact, the rat dorsal raphe receives one of the richest noradrenergic innervations in the brain (15,89,150). Overall, NE appears to be excitatory at serotonergic raphe neurons. For example, interruption of noradrenergic transmission by systemic administration of an α-adrenoceptor antagonist or iontophoretic application of an α-adrenoceptor antagonist in the vicinity of serotonergic neurons completely suppresses their spontaneous firing (14). Iontophoretic application of NE during the suppression of serotonergic cell activity produced by phentolamine or WB-4104, antagonists of α-adrenoceptors, can rapidly restore firing of these neurons to their normal activity (14). Most of the noradrenergic innervation of the VTA arises from LC neurons and noradrenergic input to the VTA is excitatory, mediated by excitatory α_1-adrenoceptors (59). In rats, chemical denervation of noradrenergic projections by DSP_4 treatment suppresses mesolimbic DA release (83) and reduces the effectiveness of positive reinforcers (109). Hence, if noradrenergic transmission is reduced, as has been hypothesized to occur in major depression, then reduced noradrenergic input to the raphe nuclei and VTA would be expected to contribute to reductions in serotonergic and dopaminergic transmission (109).

The LC and the VTA receive serotonergic terminals originating in the raphe nuclei. Serotonergic innervation to the LC originates from several sources including the dorsal and median raphe nuclei (93,108,181). The effects of 5HT on the activity of the LC are complex, and depend on whether drugs used to manipulate the serotonergic system are administered directly into the LC or whether they are administered systemically. Systemic administration of $5HT_1$ and $5HT_2$ receptor agonists or antagonists modulates the activity of the LC. These effects appear to be mediated indirectly, at least in part, rather than by actions at these receptors within the LC (30,57,64). 5HT affects LC activity, at least in part, by attenuating glutamatergic activation of the LC (8,159). Messenger RNAs encoding $5HT_{1A}$, $5HT_{1C}$, and $5HT_{2C}$ receptors are found in rat LC neurons (137,192). Interestingly, neurotoxic destruction of serotonergic terminals results in an increase in firing of the LC (71) and increases in LC mRNA and tyrosine hydroxylase activity (71). Based on these findings, the overall effect of 5HT release in the LC appears to be inhibitory.

The VTA receives afferent projections from 5HT-containing axon terminals originating in the dorsal and median raphe nuclei (70). Moreover, 5HT neurons innervate both dopaminergic and nondopaminergic (e.g., GABA) neurons in the VTA and may influence mesocortical and mesolimbic efferent systems through synaptic as well as nonsynaptic mechanisms (70). 5HT-induced release of [^{3}H]DA from rat VTA slice preparations is blocked by methysergide, but not cyproheptadine, suggesting an involvement of the $5HT_1$ receptor (17). Local application (in the VTA) of agonists at $5\text{-}HT_{1A}$ receptors increases the firing of DA neurons in the VTA (6,87) and administration of a $5HT_{1A}$ receptor agonist systemically increases DA release in the medial PFC (7). Microinfusion of 5HT into the VTA in rats results in an increased release of DA in the NAC (61). It is tempting to speculate that the firing mode of VTA DA neurons is dependent, among other factors, on the activity of serotonergic terminals originating in the raphe. Because 5HT increases extracellular DA (128), a serotonergic deficit, which has been suggested as one primary abnormality in depression, would also lead to a DA deficit.

High levels of DA are found in the dorsal raphe and LC (89). Moreover, D_2 receptors and D_2 receptor mRNA are expressed in both regions (185). Lesions of the VTA cause LC DA levels to fall by about 50%. DA neurotransmission is important for the rewarding effects of LC stimulation, without which such stimulation appears to be aversive (41). In the dorsal raphe nuclei, a moderate number of DA-immunoreactive fibers cover rather homogenously all subdivisions of the region (136). It has been postulated that dopaminergic neurotransmission to the dorsal raphe inhibits the activity of dorsal raphe neurons by increasing extracellular concentrations of 5HT in the dorsal raphe and, consequently, by increasing somatodendritic 5HT autoreceptor stimulation in this nucleus (46).

Monoamine Systems and Other Neurotransmitters

CRF

Much evidence has accumulated implicating a state of CRF hypersecretion in major depression (112,113,125). Interestingly, the LC, raphe nuclei and VTA receive moderate to dense innervation by CRF neurons. The LC receives excitatory CRF input from several sources, and these afferents appear to be topographically organized with respect to the type of information conveyed (177). The nucleus paragigantocellularis and Barrington's nucleus sends afferents directly to the nuclear elements of the LC. The LC also receives CRF input from limbic brain regions, including the central nucleus of the amygdala, as well as the bed nucleus of the stria terminalis and hypothalamic subregions (177). These limbic CRF neurons project to the peri-cerulea area, and in particular to the rostrolateral peri-LC. CRF terminals form direct contacts with noradrenergic dendrites (176). CRF, injected intracerebroventrically or directly into the LC, activates LC neurons and enhances release of NE in projection areas (163). Internal and external stressors are known to activate the LC via CRF, including colonic distension, hypotensive challenge, and foot shock. The ability of these stressors to activate the LC is blocked by CRF antagonists (32,85,104,174). In general, the pontine-medullary CRF projections to the LC are thought to coordinate cognitive and autonomic responses to internal physiologic challenges, whereas the limbic CRF projections mediate LC activation by external stressors that have emotional content (81). Interestingly, administration of a CRF antagonist blocks stress-induced increases in LC tyrosine hydroxylase (104), an effect shared by antidepressant drugs (105).

The serotonergic raphe nuclei also receive CRF innervation. CRF terminals in raphe nuclei originate from local and distant cell bodies (148,151). The effects of CRF on raphe firing are complex (77). At low doses, CRF produces primarily inhibitory effects on raphe discharge. In contrast, higher doses of CRF excite raphe neurons. Likewise, the effects of intracerebroventricularly administered CRF on striatal 5HT release are biphasic (140). Low doses of CRF decrease 5HT release in the striatum, whereas high doses increase striatal 5HT. Price and associates (140) suggest that CRF has predominantly inhibitory actions at the level of the raphe. Hence, a putative hypersecretion of CRF in major depression could contribute to the deficit in serotonergic transmission at the level of the raphe nuclei.

The VTA is densely innervated by CRF-positive fibers, whereas the substantia nigra receives only scattered CRF innervation (11). Intracerebroventricular administration of CRF to mice produces behavioral activation and a "stress-like" increase in DA metabolism in several brain regions. Direct injections of CRF into the VTA produces dose-dependent increase in locomotor activity, an affect that is not antagonized by the DA receptor blocker, haloperidol (74). Intracerebroventricular or intraperitoneal administration of low doses of CRF increases DA and DA metabolite levels in the rat medial prefrontal cortex (84). Together, these findings suggest that CRF exerts an excitatory action in the VTA. The long-term effects of CRF administration on DA metabolism have not been studied.

Substance P

Recent studies suggest that substance P antagonists may have antidepressant properties (82), although there have been questions regarding their efficacy (45). Interestingly, there is a relatively dense network of substance P immunoreactive fibers in the human LC and surrounding regions (50). Many of these fibers may originate from the nucleus of the solitary tract (50,100,145). In addition, there is a high density of binding of radiolabeled substance P to neurokinin-1 receptors in the LC (34). Substance P potently stimulates the firing of LC neurons (62). There is considerable evidence that substance P plays a role in the central response to stress (13,65). Interestingly, substance P antagonists (in particular, selective neurokinin-1 receptor antagonists), when administered intracerebroventricularly, attenuate restraint stress-induced biochemical indices of LC activation (65). Repeated administration of rats with antidepressant drugs (perhaps not all types) down-regulates substance P in several brain regions (27,158).

Substance P is co-localized with 5HT in 25% to 50% of the neurons in the human median and dorsal raphe nuclei, respectively (12,155). Substance P-containing serotonergic neurons are not randomly located within the raphe nuclei, but are localized to specific subregions, suggesting that substance P co-releases with 5HT in specific brain regions. The dorsal raphe nuclei also receive innervation from substance P-containing neurons with cell bodies occurring outside the region of the raphe (92). There is a high density of substance P receptors in the region of the dorsal raphe nuclei (91). Substance P appears to activate raphe neurons and microin-

jection of substance P into the dorsal raphe increases hippocampal levels of 5HT.

Substance P receptor mRNAs (NK1 and NK3) are found in DA neurons of the human and rat midbrain (188); substance P-immunoreactive terminals, making synaptic contacts with TH-positive neurons in the VTA, also have been demonstrated (169). Infusion of a substance P receptor agonist into the VTA stimulates locomotor activity and increases DA turnover in the nucleus accumbens (149), indicating an excitatory action of substance P on DA neurotransmission.

Glutamate

NMDA receptor antagonists have antidepressant actions in animal models of depression (129) and demonstrated antidepressant effects in humans (20). High levels of serum glutamate levels in depressed subject have been reported (2,76) with exception (1). In addition, alterations in the allosterism of NMDA receptor binding in the frontal cortex of suicide victims (115), and elevated levels of CSF glutamine (glutamate metabolite/precursor) in depressed patients have been reported (88). Such findings have led to speculation that there may be excessive glutamate neurotransmission in depressive disorders. Glutamatergic neurons provide the major excitatory neurotransmitter input to the LC. Glutamatergic innervation of the LC derives largely from the nucleus paragigantocellularis (9). Glutamate activates the LC through activation of both NDMA and non-NMDA (aspartate) receptors (117). Handling and immobilization stress increases glutamate measured in the rat LC by microdialysis (161,170). Interestingly, noise stress-induced enhancement of glutamate release in the LC is abolished by superfusion of the LC with a CRF antagonist (160), demonstrating an important interaction between CRF and glutamate systems at the level of the LC (88). It is tempting to speculate that a deficit in noradrenergic transmission in major depression is secondary to a chronic elevation in glutamatergic input into the LC and a resulting depletion of central NE.

The raphe nuclei also receive glutamatergic input. At least part of the glutamatergic input to the dorsal raphe nuclei originates in the habenula (72). As is the case for the LC, glutamate is excitatory in the raphe nuclei. The activity of DA neurons in the mesolimbic and mesocortical circuitry can also be modulated by excitatory amino acids (73). DA neurons in the VTA receive direct glutamatergic innervation from the prefrontal cortex (73). Glutamate excites DA cell activity via inotropic and metabotropic receptors (167).

GABA

There is considerable preclinical and clinical evidence that depression is associated with reduced GABA function. Petty has reviewed this topic (135). To summarize, plasma GABA is low in patients with major depression (133–135). GABA agonists have activity in animal models useful for identifying antidepressants (16,196). Finally, GABA agonists appear to have some antidepressant activity in humans (135).

GABA provides a major inhibitory input to the LC. GABAergic neurons arriving in the LC originate largely from the nucleus prepositus, stimulation of which inhibits the firing of LC neurons (44). There are apparently no GABA cell bodies intrinsic to the LC, but glutamic acid decarboxylase immunoreactive nerve terminals are present, closely juxtaposed to noradrenergic cell bodies and dendrites (22). GABA inhibits the firing of LC neurons primarily by activation of $GABA_A$ receptors (123), and these receptors have been autoradiographically identified in the LC (29, 126). The dorsal raphe nuclei receive GABAergic innervation from local interneurons and from multiple distant sources (54,184) and dorsal raphe neurons express $GABA_A$ receptors (53). Iontophoretic application of GABA strongly inhibits the firing of dorsal raphe nuclei neurons (52). DA neurons in the VTA are innervated by GABAergic afferents projecting mainly from the forebrain. GABA terminals also synapse on GABA interneurons that themselves synapse onto DA neurons (73). GABA inhibits the activity of DA neurons by acting through GABA receptors ($GABA_B$) on DA neurons (167).

INTEGRATION OF MONOAMINE AND OTHER NEUROTRANSMITTER THEORIES

Investigations of the neurochemical pathology of depressive disorders reveal abnormalities in monoamine systems as well as other neurotransmitter systems. Nevertheless, it is conceivable that a root cause of depression is a failure or deficit in a single neurotransmitter system. Because of the interconnectivity of the monoamine systems, it is likely that failure in one system to adequately respond to demand would quickly lead to compensations, or possibly failure, of the other monoamine systems, as well as changes and/or biochemical compensations of numerous systems that are directly regulated by the pathogenic neurotransmitter system. Hence, evidence suggesting that there is dysfunction of monoaminergic, as well as nonmonoaminergic, neurotransmitter systems in depression compels us to integrate neurotransmitter interactions into theoretical models of the neurochemical circuitry of depression. This is a difficult undertaking and requires translation and integration of clinical, preclinical, and basic research findings. The postulate that depression is associated with a deficiency of NE or an increase in the demand for NE (as discussed) provides a good example of concatenation of clinical/postmortem findings, experimental/laboratory animal findings, and basic research findings regarding transmitter interactions. That is, elevated tyrosine hydroxylase in the LC, as observed in major depressive suicide victims, can be experimentally pro-

duced by pharmacologically depleting NE or chronically stressing rats. Depletion of 5HT can also up-regulate tyrosine hydroxylase in the LC, as can chronic administration of CRF. Interestingly, CRF is reported to be elevated in depression, is released by stress, and CRF excites LC neurons. Together, these data suggest that elevated CRF in depression increases demand for NE, probably leading to elevated tyrosine hydroxylase expression. Elevated CRF may also contribute to reduce serotonergic transmission in depression, given the CRF can inhibit dorsal raphe neurons. Furthermore, it is conceivable that other excitatory inputs to the LC, such as substance P, might also exhibit elevated activity in depression. If so, substance P antagonists with antidepressant actions may elicit their effects on mood, at least in part, through actions at the LC. In contrast to excitatory transmitters, elevated demand for NE could also result from reduced inhibitory input to the LC. Here, of interest is the putative association of low levels of GABA with major depression (discussed in the preceding) and the fact that GABA provides an inhibitory input to the LC.

Another interesting possibility is that disruption of a single neurotransmitter system may be common to depressive disorders, whereas different mood disorders or subtypes of major depression itself may be a result of the type of altered neuronal input to that particular system. Using the hypothesis of increased demand for NE in depression as an example, elevated activity of the LC may be a result of elevated CRF input to the LC in some depressives, whereas others may experience elevated LC activity as a result of overactive substance P or glutamate input or decreased GABA input. Presently, there is little evidence to support the idea of serotonergic or noradrenergic depressives that respond selectively to serotonergic or noradrenergic antidepressant drugs, respectively. However, NE and 5HT containing neurons may be downstream of disrupted input systems that may actually differentiate subtypes of depressive disorders at a neurochemical/neuroanatomic level. Future research on neuropathology of psychiatric disorders should benefit greatly if designed to simultaneously measure multiple neurotransmitter systems. Ultimately, a thorough understanding of neurotransmitter interactions and integrated neuronal systems as they relate to the neurochemical pathology of depressive disorders will likely yield novel therapeutic interventions.

ACKNOWLEDGMENTS

Dr. Ordway has received research support from Eli Lilly, Pharmacia-Upjohn, and Merck. In addition, he served as a consultant for both Eli Lilly and Pharmacia-Upjohn.

REFERENCES

1. Altamura C, Maes M, Dai J, et al. Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. *Eur Neuropsychopharmacol* 1995;5(Suppl): 71–75.
2. Altamura CA, Mauri MC, Ferrara A, et al. Plasma and platelet excitatory amino acids in psychiatric disorders. *Am J Psychiatry* 1993;150:1731–1733.
3. Arango V, Ernsberger P, Marzuk PM, et al. Autoradiographic demonstration of increased serotonin 5-HT2 and B-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry* 1990;47:1038–1047.
4. Arango V, Ernsberger P, Sved AF, et al. Quantitative autoradiography of α_1 and α_2 adrenergic receptors in the cerebral cortex of controls and suicide victims. *Brain Res* 1993;630:271–282.
5. Arango V, Underwood MD, Mann JJ. Fewer pigmented locus ceruleus neurons in suicide victims: preliminary results. *Biol Psychiatry* 1996;39:112–120.
6. Arborelius L, Chergui K, Murase S, et al. The 5-HT1A receptor selective ligands, (R)-8-OH-DPAT and (S)-UH-301, differentially affect the activity of midbrain dopamine neurons. *Naunyn Schmiedebergs Arch Pharmacol* 1993;347:353–362.
7. Arborelius L, Nomikos GG, Hacksell U, et al. (R)-8-OH-DPAT preferentially increases dopamine release in rat medial prefrontal cortex. *Acta Physiol Scand* 1993;148:465–466.
8. Aston-Jones G, Akaoka H, Charlety P, et al. Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus ceruleus neurons. *J Neurosci* 1991;11:760–769.
9. Aston-Jones G, Ennis M, Pieribone VA, et al. The brain nucleus locus coeruleus: restricted afferent control of a broad efferent network. *Science* 1986;234:734–737.
10. Aston-Jones G, Shipley MT, Chouvet G, et al. Afferent regulation of locus ceruleus neurons: anatomy, physiology and pharmacology. *Prog Brain Res* 1991;88:47–75.
11. Austin MC, Rhodes JL, Lewis DA. Differential distribution of corticotropin-releasing hormone immunoreactive axons in monoaminergic nuclei of the human brainstem. *Neuropsychopharmacology* 1997;17:326–341.
12. Baker KG, Halliday GM, Hornung JP, et al. Distribution, morphology and number of monoamine-synthesizing and substance P-containing neurons in the human dorsal raphe nucleus. *Neuroscience* 1991;42:757–775.
13. Bannon MJ, Elliott PJ, Alpert JE, et al. Role of endogenous substance P in stress-induced activation of mesocortical dopamine neurones. *Nature* 1983;306:791–792.
14. Baraban JM, Aghajanian GK. Suppression of serotonergic neuronal firing by α-adrenoceptor antagonists: evidence against GABA mediation. *Eur J Pharmacol* 1980;66:287–294.
15. Baraban JM, Aghajanian GK. Noradrenergic innervation of serotonergic neurons in the dorsal raphe: demonstration by electron microscopic autoradiography. *Brain Res* 1981;204:1–11.
16. Bartholini G. Experimental basis for the antidepressant action of the GABA receptor agonist progabide. *Neurosci Lett* 1984; 47:351–355.
17. Beart PM, McDonald D. 5-Hydroxytryptamine and 5-hydroxytryptaminergic-dopaminergic interactions in the ventral tegmental area of rat brain. *J Pharmacol* 1982;34:591–593.
18. Becker G, Struck M, Bogdahn U, et al. Echogenicity of the brainstem raphe in patients with major depression. *Psychiatry Res* 1994;55:75–84.
19. Beckmann H, Goodwin FK. Urinary MHPG in subgroups of depressed patients and normal controls. *Neuropsychobiology* 1980;6:91–100.
20. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;47: 351–354.
21. Berman RM, Narasimhan M, Miller H, et al. Transient depressive relapse induced by catecholamine depletion. *Arch Gen Psychiatry* 1999;56:395–403.

22. Berod A, Chat M, Paut L, et al. Catecholaminergic and GABAergic anatomic relationship in the rat substantia nigra, locus coeruleus, and hypothalamic median eminence: immunocytochemical visualization of biosynthetic enzymes on serial semithin plastic-embedded sections. *J Histochem Cytochem* 1984;32:1331–1338.
23. Blier P, de Montigny C. Current advances and trends in the treatment of depression [see comments]. *Trends Pharmacol Sci* 1994;15:220–226.
24. Blier P, de Montigny C, Chaput Y. A role for the serotonin system in the mechanism of action of antidepressant treatments: peclinical evidence. *J Clin Psychiatry* 1990;5:14–20.
25. Bligh-Glover W, Kolli TN, Shapiro-Kulnane L, et al. The serotonin transporter in the midbrain of suicide victims with major depression. *Biol Psychiatry* 2000;47:1015–1024.
26. Brady LS. Stress, antidepressant drugs, and the locus coeruleus. *Brain Res Bull* 1994;35:545–556.
27. Brodin E, Ogren SO, Theodorsson-Norheim E. Effects of subchronic treatment with imipramine, zimelidine and alaproclate on regional tissue levels of substance P- and neurokinin A/neurokinin B-like immunoreactivity in the brain and spinal cord of the rat. *Neuropharmacology* 1987;26:581–590.
28. Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. [Review] [22 refs]. *J Clin Psychiatry* 1998;59(Suppl 14):11–14.
29. Cheetham SC, Crompton MR, Katona CL, et al. Brain GABAA/benzodiazepine binding sites and glutamic acid decarboxylase activity in depressed suicide victims. *Brain Res* 1988; 460:114–123.
30. Chiang C, Aston-Jones G. A 5-hydroxytryptamine2 agonist augments gamma-aminobutyric acid and excitatory amino acid inputs to noradrenergic locus ceruleus neurons. *Neuroscience* 1993;54:409–420.
31. Cubells JF, Kim KS, Baker H, et al. Differential in vivo regulation of mRNA encoding the norepinephrine transporter and tyrosine hydroxylase in rat adrenal medulla and locus ceruleus. *J Neurochem* 1995;65:502–509.
32. Curtis AL, Grigoriadis DE, Page ME, et al. Pharmacologic comparison of two corticotropin-releasing factor antagonists: in vivo and in vitro studies. *J Pharmacol Exp Ther* 1994;268:359–365.
33. D'haenen HA, Bossuyt A. Dopamine D2 receptors in depression measured with single photon emission computed tomography. *Biol Psychiatry* 1994;35:128–132.
34. Dam TV, Martinelli B, Quirion R. Autoradiographic distribution of brain neurokinin-1/substance P receptors using a highly selective ligand [^{3}H]-[Sar9,Met(O2)11]-substance P. *Brain Res* 1990;531:333–337.
35. Delgado PL. Depression: the case for a monoamine deficiency. *J Clin Psychiatry* 2000;61(Suppl 6):7–11.
36. Delgado PL, Price LH, Miller HL, et al. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. *Arch Gen Psychiatry* 1994;51: 865–874.
37. Demontis MG, Fadda P, Devoto P, et al. Sleep deprivation increases dopamine D1 receptor antagonist [3H]SCH 23390 binding and dopamine-stimulated adenylate cyclase in the rat limbic system. *Neurosci Lett* 1990;117:224–227.
38. Drevets WC, Frank E, Price JC, et al. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 1999;46: 1375–1387.
39. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression [see comments]. *Arch Gen Psychiatry* 1997; 54:597–606.
40. Durlach–Misteli C, Van Ree JM. Dopamine and melatonin in the nucleus accumbens may be implicated in the mode of action of antidepressant drugs. *Eur J Pharmacol* 1992;217:15–21.
41. Duvauchelle CL, MacConell LA, Eremia AD, et al. Pimozide prevents the development of conditioned place preferences induced by rewarding locus ceruleus stimulation. *Behav Brain Res* 1992;50:85–92.
42. Dziedzicka-Wasylewska M, Rogoz R, Klimek V, et al. Repeated administration of antidepressant drugs affects the levels of mRNA coding for D1 and D2 dopamine receptors in the rat brain. *J Neural Transm* 1997;104:515–524.
43. Ebert D, Feistel H, Loew T, et al. Dopamine and depression—striatal dopamine D2 receptor SPECT before and after antidepressant therapy. *Psychopharmacology (Berl)* 1996;126: 91–94.
44. Ennis M, Aston-Jones G. GABA-mediated inhibition of locus ceruleus from the dorsomedial rostral medulla. *J Neurosci* 1989; 9:2973–2981.
45. Enserink M. Can the placebo be the cure? [news] [see comments]. *Science* 1999;284:238–240.
46. Ferre' S, Cor'tes R, Artigas F. Dopaminergic regulation of the serotonergic raphe-striatal pathway: microdialysis studies in freely moving rats. *J Neurosci* 1994;14(8):4839–4846.
47. Ferrier IN, McKeith IG, Cross AJ, et al. Postmortem neurochemical studies in depression. *Ann N Y Acad Sci* 1986;487: 128–142.
48. Fibiger HC, Phillips AG. Mesocorticolimbic dopamine systems and reward. *Ann N Y Acad Sci* 1988;537:206–215.
49. Flory JD, Mann JJ, Manuck SB, et al. Recovery from major depression is not associated with normalization of serotonergic function. *Biol Psychiatry* 1998;43:320–326.
50. Fodor M, Gorcs TJ, Palkovits M. Immunohistochemical study on the distribution of neuropeptides within the pontine tegmentum—particularly the parabrachial nuclei and the locus ceruleus of the human brain. *Neuroscience* 1992;46:891–908. [Published erratum appears in *Neuroscience* 1992;48(3):753.]
51. Foote SL, Bloom FE, Aston-Jones G. Nucleus locus coeruleus: new evidence of anatomic and physiological specificity. *Physiol Rev* 1983;63:844–914.
52. Gallager DW. Benzodiazepines: potentiation of a GABA inhibitory response in the dorsal raphe nucleus. *Eur J Pharmacol* 1978; 49:133–143.
53. Gao B, Fritschy JM, Benke D, et al. Neuron-specific expression of GABAA-receptor subtypes: differential association of the alpha 1- and alpha 3-subunits with serotonergic and GABAergic neurons. *Neuroscience* 1993;54:881–892.
54. Gervasoni D, Peyron C, Rampon C, et al. Role and origin of the GABAergic innervation of dorsal raphe serotonergic neurons. *J Neurosci* 2000;20:4217–4225.
55. Gibbons RD, Davis JM. Consistent evidence for a biological subtype of depression characterized by low CSF monoamine levels. *Acta Psychiatr Scand* 1986;74:8–12.
56. Golden RN, Ekstrom D, Brown TM, et al. Neuroendocrine effects of intravenous clomipramine in depressed patients and healthy subjects. *Am J Psychiatry* 1992;149:1168–1175.
57. Gorea E, Davenne D, Lanfumey L, et al. Regulation of noradrenergic coerulean neuronal firing mediated by 5-HT2 receptors: involvement of the prepositus hypoglossal nucleus. *Neuropharmacology* 1991;30:1309–1318.
58. Grant MM, Weiss JM. Effects of chronic antidepressant drug administration and electroconvulsive shock and locus ceruleus electrophysiological activity. *Biol Psychiatry* 2001;49:117–129.
59. Grenhoff J, Svensson TH. Prazosin modulates the firing pattern of dopamine neurons in rat ventral tegmental area. *Eur J Pharmacol* 1993;233:79–84.
60. Gross G, Gothert M, Glapa U, et al. Lesioning of serotoninergic and noradrenergic nerve fibres of the rat brain does not decrease binding of ^{3}H-clonidine and ^{3}H-rauwolscine to cortical mem-

branes. *Naunyn-Schmiedeberg's Arch Pharmacol* 1985;328: 229–235.
61. Guan XM, McBride WJ. Serotonin microinfusion into the ventral tegmental area increases accumbens dopamine release. *Brain Res Bull* 1989;23:541–547.
62. Guyenet PG, Aghajanian GK. Excitation of neurons in the nucleus locus ceruleus by substance P and related peptides. *Brain Res* 1977;136:178–184.
63. Haddjeri N, Blier P, de Montigny C. Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. *J Neurosci* 1998;18:10150–10156.
64. Haddjeri N, de Montigny C, Blier P. Modulation of the firing activity of noradrenergic neurones in the rat locus ceruleus by the 5-hydroxtryptamine system. *Br J Pharmacol* 1997;120: 865–875.
65. Hahn MK, Bannon MJ. Stress-induced C-fos expression in the rat locus ceruleus is dependent on neurokinin 1 receptor activation. *Neuroscience* 1999;94:1183–1188.
66. Halaris AE, Belendiuk KT, Freedman DX. Antidepressant drugs affect dopamine uptake. *Biochem Pharmacol* 1975;24: 1896–1897.
67. Harro J, Oreland L. Depression as a spreading neuronal adjustment disorder. *Eur Neuropsychopharmacol* 1996;6:207–223.
68. Heimer L, Alheid GF, De Olmos JS, et al. The accumbens: beyond the core-shell dichotomy. *J Neuropsychiatry Clin Neurosci* 1997;9:354–381.
69. Heninger GR, Charney DS, Sternberg DE. Serotonergic function in depression. Prolactin response to intravenous tryptophan in depressed patients and healthy subjects. *Arch Gen Psychiatry* 1984;41:398–402.
70. Herve D, Pickel VM, Joh TH, et al. Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. *Brain Res* 1987;435:71–83.
71. Kaehler ST, Singewald N, Philippu A. Dependence of serotonin release in the locus ceruleus on dorsal raphe neuronal activity. *Naunyn Schmiedebergs Arch Pharmacol* 1999;359:386–393.
72. Kalen P, Pritzel M, Nieoullon A, et al. Further evidence for excitatory amino acid transmission in the lateral habenular projection to the rostral raphe nuclei: lesion-induced decrease of high affinity glutamate uptake. *Neurosci Lett* 1986;68:35–40.
73. Kalivas PW, Churchill L, Klitenick MA. The circuitry mediating the translation of motivational stimuli into adaptive motor responses. In: Kalivas PW, Barnes CD, eds. *Limbic motor circuits and neuropsychiatry.* Boca Raton, FL: CRC Press, 1993: 237–287.
74. Kalivas PW, Duffy P, Latimer LG. Neurochemical and behavioral effects of corticotropin-releasing factor in the ventral tegmental area of the rat. *J Pharmacol Exp Ther* 1987;242: 757–763.
75. Kalivas PW, Nakamura M. Neural systems for behavioral activation and reward. *Curr Opin Neurobiol* 1999;9:223–227.
76. Kim JS, Schmid-Burgk W, Claus D, et al. Effects of amitriptyline on serum glutamate and free tryptophan in rats. *Arch Psychiatr Nervenkr* 1982;232:391–394.
77. Kirby LG, Rice KC, Valentino RJ. Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. *Neuropsychopharmacology* 2000;22:148–162.
78. Klimek V, Maj J. Repeated administration of antidepressants enhances agonist affinity for mesolimbic D2-receptors. *J Pharm Pharmacol* 1989;41:555–558.
79. Klimek V, Rajkowska G, Luker SN, et al. Brain noradrenergic receptors in major depression and schizophrenia. *Neuropsychopharmacology* 1999;21:69–81.
80. Klimek V, Stockmeier CA, Overholser JC, et al. Reduced levels of norepinephrine transporters in the locus ceruleus in major depression. *J Neurosci* 1997;17:8451–8458.
81. Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiatry* 1999;46:1167–1180.
82. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors [see comments]. *Science* 1998;281:1640–1645.
83. Lategan AJ, Marien MR, Colpaert FC. Suppression of nigrostriatal and mesolimbic dopamine release in vivo following noradrenaline depletion by DSP-4: a microdialysis study. *Life Sci* 1992;50:995–999.
84. Lavicky J, Dunn AJ. Corticotropin-releasing factor stimulates catecholamine release in hypothalamus and prefrontal cortex in freely moving rats as assessed by microdialysis. *J Neurochem* 1993;60:602–612.
85. Lechner SM, Curtis AL, Brons R, et al. Locus ceruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. *Brain Res* 1997;756:114–124.
86. Lee C-M, Javitch JA, Snyder SH. Recognition sites for norepinephrine uptake: regulation by neurotransmitter. *Science* 1983; 220:626–629.
87. Lejeune F, Millan MJ. Induction of burst firing in ventral tegmental area dopaminergic neurons by activation of serotonin (5-HT)1A receptors: WAY 100,635-reversible actions of the highly selective ligands, flesinoxan and S 15535. *Synapse* 1998; 30:172–180.
88. Levine J, Panchalingam K, Rapoport A, et al. Increased cerebrospinal fluid glutamine levels in depressed patients. *Biol Psychiatry* 2000;47:586–593.
89. Levitt P, Moore RY. Origin and organization of brain stem catecholamine innervation in the rat. *J Comp Neurol* 1979;186: 505–528.
90. Little KY, McLauglin DP, Ranc J, et al. Serotonin transporter binding sites and mRNA levels in depressed persons committing suicide. *Biol Psychiatry* 1997;41:1156–1164.
91. Liu RP, Swenberg ML. Autoradiographic localization of substance P ligand binding sites and distribution of immunoreactive neurons in the periaqueductal gray of the rat. *Brain Res* 1988; 475:73–79.
92. Lorens SA, Paris JM, Brodin E. Neurokinin innervation of the rat median raphe nucleus does not originate in the brain stem. *Ann NY Acad Sci* 1991;632:431–434.
93. Maeda T, Kojima Y, Arai R, et al. Monoaminergic interaction in the central nervous system: a morphological analysis in the locus ceruleus of the rat. *Comp Biochem Physiol C* 1991;98: 193–202.
94. Maj J, Rogoz Z, Skuza G, et al. Repeated treatment with antidepressant drugs increases the behavioural response to apomorphine. *J Neural Transm* 1984;60:273–282.
95. Maj J, Rogoz Z, Skuza G, et al. Repeated treatment with antidepressant drugs potentiates the locomotor response to (+)-amphetamine. *J Pharm Pharmacol* 1984;36:127–130.
96. Maj J, Wedzony K, Klimek V. Desipramine given repeatedly enhances behavioural effects of dopamine and *d*-amphetamine injected into the nucleus accumbens. *Eur J Pharmacol* 1987; 140:179–185.
97. Malison RT, Price LH, Berman R, et al. Reduced brain serotonin transporter availability in major depression as measured by [^{123}I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography [see comments]. *Biol Psychiatry* 1998;44:1090–1098.
98. Mann JJ. Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. *Neuropsychopharmacology* 1999;21:99S–105S.
99. Mann JJ, Malone KM, Psych MR, et al. Attempted suicide characteristics and cerebrospinal fluid amine metabolites in depressed inpatients. *Neuropsychopharmacology* 1996;15: 576–586.

100. Mantyh PW, Hunt SP. Neuropeptides are present in projection neurones at all levels in visceral and taste pathways: from periphery to sensory cortex. *Brain Res* 1984;299:297–312.
101. Martensson B, Nyberg S, Toresson G, et al. Fluoxetine treatment of depression. Clinical effects, drug concentrations and monoamine metabolites and N-terminally extended substance P in cerebrospinal fluid. *Acta Psychiat Scand* 1989;79:586–596.
102. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci* 1997;9:471–481.
103. McKeith IG, Marshall EF, Ferrier IN, et al. 5-HT receptor binding in postmortem brain from patients with affective disorder. *J Affect Disord* 1987;13:67–74.
104. Melia KR, Duman RS. Involvement of corticotropin-releasing factor in chronic stress regulation of the brain noradrenergic system. *Proc Natl Acad Sci USA* 1991;88:8382–8386.
105. Melia KR, Nestler EJ, Duman RS. Chronic imipramine treatment normalizes levels of tyrosine hydroxylase in the locus ceruleus of chronically stressed rats. *Psychopharmacology* 1992;108: 23–26.
106. Melia KR, Rasmussen K, Terwilliger RZ, et al. 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* 1992;58: 494–502.
107. Mongeau R, de Montigny C, Blier P. Electrophysiologic evidence for desensitization of alpha 2-adrenoceptors on serotonin terminals following long-term treatment with drugs increasing norepinephrine synaptic concentration. *Neuropsychopharmacology* 1994;10:41–51.
108. Morgane PJ, Jacobs MS. Raphe projections to the locus ceruleus in the rat. *Brain Res Bull* 1979;4:519–534.
109. Morley MJ, Shah K, Bradshaw CM, et al. DSP4 and Herrnstein's equation: further evidence for a role of noradrenaline in the maintenance of operant behaviour by positive reinforcement. *Psychopharmacology (Berl)* 1988;96:551–556.
110. Nankova B, Kvetnansky R, Hiremagalur B, et al. Immobilization stress elevates gene expression for catecholamine biosynthetic enzymes and some neuropeptides in rat sympathetic ganglia: effects of adrenocorticotropin and glucocorticoids. *Endocrinology* 1996;137:5597–5604.
111. Nemeroff CB. The role of corticotropin-releasing factor in the pathogenesis of major depression. [Review]. *Pharmacopsychiatry* 1988;21:76–82.
112. Nemeroff CB, Owens MJ, Bissette G, et al. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch Gen Psychiatry* 1988;45:577–579.
113. Nemeroff CB, Widerlov E, Bissette G, et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* 1984;226:1342–1344.
114. Nestler EJ, McMahon A, Sabban EL, et al. Chronic antidepressant administration decreases the expression of tyrosine hydroxylase in the rat locus coeruleus. *Proc Natl Acad Sci USA* 1990; 87:7522–7526.
115. Nowak G, Ordway GA, Paul IA. Alterations in the *N*-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res* 1995;675:157–164.
116. Oades RD, Halliday GM. Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. *Brain Res* 1987; 434:117–165.
117. Olpe H, Steinmann MW, Brugger F, et al. Excitatory amino acid receptors in rat locus coeruleus. *Naunyn-Schmiedeberg's Arch Pharmacol* 1989;339:312–314.
118. Ordway GA, Farley IJ, Dilley GE, et al. Quantitative distribution of monoamine oxidase A in brainstem monoamine nuclei is normal in major depression. *Brain Res* 1999;847:71–79.
119. Ordway GA, Schenck JE, Dilley GE, et al. Increased p-[^{125}I]iodoclonidine binding to α_2-adrenoceptors in the locus ceruleus in major depression. *Soc Neurosci Abs* 1999;2139.
120. Ordway GA, Smith KS, Haycock JW. Elevated tyrosine hydroxylase in the locus ceruleus of suicide victims. *J Neurochem* 1994; 62:680–685.
121. Ordway GA, Stockmeier CA, Cason GW, et al. Pharmacology and distribution of norepinephrine transporters in the human locus ceruleus and raphe nuclei. *J Neurosci* 1997;17: 1710–1719.
122. Ordway GA, Widdowson PS, Smith KS, et al. Agonist binding to α_2-adrenoceptors is elevated in the locus ceruleus from victims of suicide. *J Neurochem* 1994;63:617–624.
123. Osmanovic SS, Shefner SA. γ-Aminobutyric acid responses in rat locus ceruleus neurones in vitro: a current-clamp and voltage-clamp study. *J Physiol* 1990;421:151–170.
124. Osterhout CA, Chikaraishi DM, Tank AW. Induction of tyrosine hydroxylase protein and a transgene containing tyrosine hydroxylase 5′ flanking sequences by stress in mouse adrenal gland. *J Neurochem* 1997;68:1071–1077.
125. Owens MJ, Nemeroff CB. Preclinical and clinical studies with corticotropin-releasing factor: implications for affective disorders. [Review]. *Psychopharmacology Bull* 1988;24:355–359.
126. Palacios, J. M., Wamsley, J. K., and Kuhar, M. J. High affinity GABA receptors—autoradiographic localization. *Brain Res* 1981;222:285–307.
127. Papp M, Klimek V, Willner P. Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress-induced anhedonia and its reversal by imipramine. *Psychopharmacology (Berl)* 1994;115:441–446.
128. Parsons LH, Justice JBJ. Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. *Brain Res* 1993;606:195–199.
129. Paul IA. NMDA receptors and affective disorders. In: Skolnick P, ed. *Antidepressants: new pharmacologic strategies.* Totowa, NJ: Humana Press, 1997:145–148.
130. Pavcovich LA, Cancela LM, Volosin M, et al. Chronic stress-induced changes in locus ceruleus neuronal activity. *Brain Res Bull* 1990;24:293–296.
131. Paykel ES, Myers JK, Dienelt MN, et al. Life events and depression. A controlled study. *Arch Gen Psychiatry* 1969;21: 753–760.
132. Petty F. GABA and mood disorders: a brief review and hypothesis. *J Affect Disord* 1995;34:275–281.
133. Petty F, Kramer GL, Gullion CM, et al. Low plasma gamma-aminobutyric acid levels in male patients with depression. *Biol Psychiatry* 1992;32:354–363.
134. Petty F, Schlesser MA. Plasma GABA in affective illness. A preliminary investigation. *J Affect Disord* 1981;3:339–343.
135. Petty F, Sherman AD. Plasma GABA levels in psychiatric illness. *J Affect Disord* 1984;6:131–138.
136. Peyron C, Luppi PH, Kitahama K, et al. Origin of the dopaminergic innervation of the rat dorsal raphe nucleus. *Neuroreport* 1995;6:2527–2531.
137. Pompeiano M, Palacios JM, Mengod G. Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT2A and 5-HT2C receptors. *Mol Brain Res* 1994;23: 163–178.
138. Potter WZ, Grossman G, Rudorfer MV. *Noradrenergic function in depressive disorders. Part A: A systems perspective.* New York: Plenum, 1993:1–27.
139. Prange AJ Jr. The pharmacology and biochemistry of depression. *Dis Nerv Syst* 1964;25:217–221.
140. Price ML, Curtis AL, Kirby LG, et al. Effects of corticotropin-releasing factor on brain serotonergic activity. *Neuropsychopharmacology* 1998;18:492–502.
141. Prisco S, Pagannone S, Esposito E. Serotonin-dopamine interac-

tion in the rat ventral tegmental area: an electrophysiological study in vivo. *J Pharmacol Exp Ther* 1994;271:83–90.
142. Qian Y, Melikian HE, Rye DB, et al. Identification and characterization of antidepressant-sensitive serotonin transporter proteins using site-specific antibodies. *J Neurosci* 1995;15: 1261–1274.
143. Randrup A, Munkvad I, Fog R, et al. Mania, depression and brain dopamine. In: Essman WB, Valzelli L, eds. *Current developments in psychopharmacology,* volume 2. New York: Spectrum, 1975:206–248.
144. Reddy PL, Khanna S, Subhash MN, et al. CSF amine metabolites in depression. *Biol Psychiatry* 1992;31:112–118.
145. Riche D, De Pommery J, Menetrey D. Neuropeptides and catecholamines in efferent projections of the nuclei of the solitary tract in the rat. *J Comp Neurol* 1990;293:399–424.
146. Rogoz R, Dziedzicka-Wasylewska M. Effects of antidepressant drugs on the dopamine D2/D3 receptors in the rat brain differentiated by agonist and antagonist binding—an autoradiographic analysis. *Naunyn Schmiedebergs Arch Pharmacol* 1999; 359:178–186.
147. Roy A, Pickar D, Linnoila M, et al. Plasma norepinephrine level in affective disorders: relationship to melancholia. *Arch Gen Psychiatry* 1985;42:1181–1185.
148. Ruggiero DA, Underwood MD, Rice PM, et al. Corticotropic-releasing hormone and serotonin interact in the human brainstem: behavioral implications. *Neuroscience* 1999;91: 1343–1354.
149. Rupniak NM, Kramer MS. Discovery of the antidepressant and anti-emetic efficacy of substance P receptor (NK1) antagonists. *Trends Pharmacol Sci* 1999;20:485–490.
150. Saavedra JM, Grobecker H, Zivin J. Catecholamines in the raphe nuclei of the rat. *Brain Res.* 1976;114:339–345.
151. Sakai K, Salvert D, Touret M, et al. Afferent connections of the nucleus raphe dorsalis in the cat as visualized by the horseradish peroxidase technique. *Brain Res* 1977;137:11–35.
152. Salomon R, Miller HL, Krystal JH, et al. Lack of behavioral effects of monoamine depletion in healthy subjects. *Biol Psychiatry* 1997;41:58–64.
153. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 1965; 122:509–522.
154. Schultzberg M, Austin MC, Crawley JN, et al. Repeated administration of desmethylimipramine blocks reserpine-induced increase in tyrosine hydroxylase mRNA in locus ceruleus neurons of the rat. *Mol Brain Res* 1991;10:307–314.
155. Sergeyev V, Hokfelt T, Hurd Y. Serotonin and substance P coexist in dorsal raphe neurons of the human brain. *Neuroreport* 1999;10:3967–3970.
156. Serra G, Collu M, D'Aquila PS, et al. Possible role of dopamine D1 receptor in the behavioural supersensitivity to dopamine agonists induced by chronic treatment with antidepressants. *Brain Res* 1990;527:234–243.
157. Shah PJ, Ogilvie AD, Goodwin GM, et al. Clinical and psychometric correlates of dopamine D2 binding in depression. *Psychol Med* 1997;27:1247–1256.
158. Shirayama Y, Mitsushio H, Takashima M, et al. Reduction of substance P after chronic antidepressants treatment in the striatum, substantia nigra and amygdala of the rat. *Brain Res* 1996;739:70–78.
159. Singewald N, Kaehler ST, Hemeida R, et al. Influence of excitatory amino acids on basal and sensory stimuli-induced release of 5-HT in the locus coeruleus. *Br J Pharmacol* 1998;123: 746–752.
160. Singewald N, Zhou GY, Chen F, et al. Corticotropin-releasing factor modulates basal and stress-induced excitatory amino acid release in the locus ceruleus of conscious rats. *Neurosci Lett* 1996;204:45–48.
161. Singewald N, Zhou GY, Schneider C. Release of excitatory and inhibitory amino acids from the locus ceruleus of conscious rats by cardiovascular stimuli and various forms of acute stress. *Brain Res* 1995;704:42–50.
162. Skolnick P, Layer RT, Popik P, et al. Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry* 1996;29:23–26.
163. Smagin GN, Swiergiel AH, Dunn AJ. Corticotropin-releasing factor administered into the locus coeruleus, but not the parabrachial nucleus, stimulates norepinephrine release in the prefrontal cortex. *Brain Res Bull* 1995;36:71–76.
164. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan [see comments]. *Lancet* 1997; 349:915–919.
165. Stockmeier CA, Dilley GE, Shapiro LA, et al. Serotonin receptors in suicide victims with major depression. *Neuropsychopharmacology* 1997;16:162–173.
166. Stockmeier CA, Shapiro LA, Dilley GE, et al. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression—postmortem evidence for decreased serotonin activity. *J Neurosci* 1998;18:7394–7401.
167. Swerdlow NR, Koob GF. Dopamine, schizophrenia, mania, and depression: toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behav Brain Sci* 1987;10:197–245.
168. Szabo ST, de Montigny C, Blier P. Progressive attenuation of the firing activity of locus ceruleus noradrenergic neurons by sustained administration of selective serotonin reuptake inhibitors. *Int J Neuropsychopharmacology* 2000;3:1–11.
169. Tamiya R, Hanada M, Kawai Y, et al. Substance P afferents have synaptic contacts with dopaminergic neurons in the ventral tegmental area of the rat. *Neurosci Lett* 1990;110:11–15.
170. Timmerman W, Cisci G, Nap A, et al. Effects of handling on extracellular levels of glutamate and other amino acids in various areas of the brain measured by microdialysis. *Brain Res* 1999; 833:150–160.
171. Torack RM, Morris JC. The association of ventral tegmental area histopathology with adult dementia. *Arch Neurol* 1988;45: 497–501.
172. U'Prichard DC, Bechtel WD, Rouot BM, et al. Multiple apparent alpha-noradrenergic receptor binding sites in rat brain: effect of 6-hydroxydopamine. *Mol Pharmacol* 1979;16:47–60.
173. Underwood MD, Khaibulina AA, Ellis SP, et al. Morphometry of the dorsal raphe nucleus serotonergic neurons in suicide victims. *Biol Psychiatry* 1999;46:473–483.
174. Valentino RJ, Page ME, Curtis AL. Activation of noradrenergic locus ceruleus neurons by hemodynamic stress is due to local release of corticotropin-releasing factor. *Brain Res* 1991;555: 25–34.
175. Van Bockstaele EJ, Aston-Jones G. Collateralized projections from neurons in the rostral medulla to the nucleus locus coeruleus, the nucleus of the solitary tract and the periaqueductal gray. *Neuroscience* 1992;49:653–668.
176. Van Bockstaele EJ, Colago EE, Valentino RJ. Corticotropin-releasing factor-containing axon terminals synapse onto catecholamine dendrites and may presynaptically modulate other afferents in the rostral pole of the nucleus locus ceruleus in the rat brain. *J Comp Neurol* 1996;364:523–534.
177. Van Bockstaele EJ, Colago EE, Valentino RJ. Amygdaloid corticotropin-releasing factor targets locus ceruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. *J Neuroendocrinol* 1998;10:743–757.
178. Van Praag HM. Indoleamines in depression. In: Usdin E, et al, eds. *Neuroregulators and psychiatric disorders.* New York: Oxford University Press, 1977:163–176.

179. Van Praag HM. New evidence of serotonin-deficient depressions. *Neuropsychobiology* 1977;3:56–63.
180. Veith R, Lewis N, Linares O, et al. Sympathetic nervous system activity in major depression: basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psychiatry* 1994;51:411–422.
181. Vertes RP, Kocsis B. Projections of the dorsal raphe nucleus to the brainstem: PHA-L analysis in the rat. *J Comp Neurol* 1994; 340:11–26.
182. Waddington JL, Deveney AM. Dopamine receptor multiplicity: "D1-like"- "D2-like" interactions and "D1-like" receptors not linked to adenylate cyclase. *Biochem Soc Trans* 1996;24: 177–182.
183. Wang P, Kitayama I, Nomura J. Tyrosine hydroxylase gene expression in the locus ceruleus of depression-model rats and rats exposed to short- and long-term forced walking stress. *Life Sci* 1998;62:2083–2092.
184. Wang QP, Ochiai H, Nakai Y. GABAergic innervation of serotonergic neurons in the dorsal raphe nucleus of the rat studied by electron microscopy double immunostaining. *Brain Res Bull* 1992;29:943–948.
185. Weiner DM, Levey AI, Sunahara RK, et al. D1 and D2 dopamine receptor mRNA in rat brain. *Proc Natl Acad Sci USA* 1991;88:1859–1863.
186. Weiss JM, Bonsall RW, Demetrikopoulos MK, et al. Galanin: a significant role in depression? *Ann NY Acad Sci* 1998;863: 364–382.
187. Weiss JM, Glazer HI, Pohorecky LA. Coping behavior and neurochemical changes: An alternative explanaion for the original "learned helplessness" experiments. In: Kling SG, ed. *Animal models in human psychobiology.* New York: Plenum, 1976: 133–145.
188. Whitty CJ, Paul MA, Bannon MJ. Neurokinin receptor mRNA localization in human midbrain dopamine neurons. *J Comp Neurol* 1997;382:394–400.
189. Willner P. Dopamine and depression: a review of recent evidence. I. Empirical studies. *Brain Res* 1983a;287:211–224.
190. Willner P. Dopamine and depression: a review of recent evidence. II. Theoretical approaches. *Brain Res* 1983b;287: 225–236.
191. Willner P. Animal models as simulations of depression. *TiPS* 1991;12:131–136.
192. Wright DE, Seroogy KB, Lundgren KH, et al. Comparative localization of serotonin 1A, 1C, and 2 receptor subtype mRNAs in rat brain. *J Comp Neurol* 1995;351:357–373.
193. Zacharko RM, Bowers WJ, Anisman H. Responding for brain stimulation: stress and desmethylimipramine. *Prog Neuropsychopharmacol Biol Psychiatry* 1984;8:601–606.
194. Zahm DS. Is the caudomedial shell of the nucleus accumbens part of the extended amygdala? A consideration of connections. *Crit Rev Neurobiol* 1998;12:245–265.
195. Zhu M–Y, Klimek V, Dilley GE, et al. Elevated levels of tyrosine hydroxylase in the locus ceruleus in major depression. *Biol Psychiatry* 1999;46:1275–1286.
196. Zivkovic B, Scatton B, Worms P, et al. Pharmacologic and therapeutic actions of GABA receptor agonists. *J Neural Transm Suppl* 1983;18:319–326.

Neuropsychopharmacology: The Fifth Generation of Progress. Edited by Kenneth L. Davis, Dennis Charney, Joseph T. Coyle, and Charles Nemeroff. American College of Neuropsychopharmacology © 2002.