HANDBOOK OF DEPRESSION

Second Edition

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CHAPTER 9

Neurobiological Aspects of Depression

Michael E. Thase

Since antiquity, there have been speculations about the biological basis of depression. To take but one example, the term *melancholia*, which is currently used to describe one of the most severe forms of depression, reflects the ancient Greek theory that mood disorders were caused by an imbalance of black bile (Jackson, 1986). Only during the past 50 years, however, has the methodology been available to study directly alterations in brain function associated with depression. What has emerged from this half-century of research has been an iterative and evolving process, answering some questions and opening new and more sophisticated lines of inquiry. One certainty is that the heterogeneous conditions grouped together under the construct of *clinical depression* are biopsychosocial disorders that—much more often than not—have multifactorial causality.

My colleagues and I reviewed evidence pertaining to neurobiological disturbances associated with depression in the previous volume of this *Handbook*, including a wide range of neurochemical, neuroendocrine, neurophysiological, and neuroanatomical parameters (Thase, Jindal, & Howland, 2002). Over the past two decades, various hypotheses have been advanced, tested, and either rejected or modified as research paradigms have evolved and knowledge about the function of the central nervous system (CNS) in health, in disease, and in response to various states of duress has grown. A number of new hypotheses also have been advanced. Some research tools, such as measurement of catecholamine metabolites in urine, blood, and cerebrospinal fluid (CSF) or electrophysiological recordings of neuronal activity, that were *de rigueur* in the 1970s and 1980s are now seldom used; others that were not technologically feasible, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) imaging of receptor binding, and fast through-put genotyping, are now commonplace.

Perhaps the most notable advances have come from research on the intracellular processes that link receptors, second messengers, and various transcription factors to the up- or down-regulation of gene activity. Elsewhere in this volume, the current status of research on the genetics (Levinson, Chapter 8, this volume) and studies using brain imaging techniques

to examine normal and pathological processes that accompany emotional expression (Davidson, Pizzagalli, & Nitschke, Chapter 10, this volume) is reviewed in detail. In this chapter, research using other neurobiological paradigms is emphasized, with a particular focus on developments that have taken place since our last comprehensive review of this literature (Thase et al., 2002). The overarching conceptual framework of this review centers on two basic tenets: (1) Clinical forms of depression comprise a related yet heterogeneous group of syndromes associated with disturbances of the brain systems that regulate the normal processes of mood, cognition, and appetitive behavior; and (2) most—if not all—forms of depression involve dysfunctional adaptations of the brain systems that regulate adaptations to stress.

BACKGROUND

Research on the neurobiology of depression began in earnest in the late 1950s, when converging lines of evidence pointed to the possibility of dysfunction of CNS systems subserved by the monoamine neurotransmitters, particularly the catecholamine norepinephrine (NE) and the indoleamine serotonin (also known as 5-hydroxytryptamine, or 5-HT). Early studies indicated that these neurotransmitters are important regulators of bodily functions that are commonly disturbed in depression, including sleep, appetite, libido, and psychomotor tone; by the mid-1960s, there was strong evidence that both types of medication used to treat depression, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), directly affect NE and/or 5-HT neurons.

Because the TCAs and MAOIs immediately increased the amount of monoamine activity at neuronal synapses, researchers initially thought that depression was caused by a deficit of 5-HT or NE activity, and presumed that mania was caused by increased NE activity, perhaps in the context of a deficit of counterbalancing 5-HT activity (Bunney & Davis, 1965; Glassman, 1969; Schildkraut, 1965). Although the role of a third monoamine neurotransmitter, dopamine (DA), was generally thought to be more relevant to psychosis and to the activity of the phenothiazine-type medications used to treat schizophrenia, some theorists also emphasized the putative role of DA in symptoms such as fatigue, anhedonia, and psychomotor retardation (Korf & van Praag, 1971). Research over the next two decades failed to support the most simplistic models (e.g., deficit states corrected by medications that "restored" neuronal monoaminergic activity), but it confirmed that the therapeutic effects of antidepressants were initiated by actions on 5-HT and/or NE neurons, and investigators documented disturbed monoaminergic function in subgroups of individuals with mood disorders (e.g., see Duman, Heninger, & Nestler, 1997; Maes & Meltzer, 1995; Nemeroff, 1998; Schatzberg & Schildkraut, 1995; Willner, 1995).

Three findings from the first generation of research on the neurobiology of depression have ongoing relevance. First, although depression is no longer thought to be caused by deficits of NE or 5-HT, it is true that subgroups of patients with depression have either low urinary levels of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (Ressler & Nemeroff, 1999; Schatzberg & Schildkraut, 1995) or low CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Maes & Meltzer, 1995). These findings have ongoing import, because the former abnormality is associated with psychomotor retardation (and, possibly, with preferential response to antidepressants that strongly affect noradrenergic neurotransmission; Schatzberg & Schildkraut, 1995), whereas low CSF 5-HIAA has been associated with increased risk of suicide, potentially lethal suicide attempts, and other

violent, life-threatening behaviors (Maes & Meltzer, 1995; Mann, Brent, & Arango, 2001), although not with preferential response to medications that powerfully affect 5-HT neurons (Maes & Meltzer, 1995). Low CSF 5-HIAA levels subsequently have been shown to be at least partly under heritable control and, across primate species, appear to be a trait-like phenomenon associated with various types of aggressivity and impulsivity (Mann et al., 2001).

A second enduring and well-replicated finding concerns the hypersecretion of the glucocorticoid hormone *cortisol*, the primary effector of stress responses of humans. Cortisol is synthesized in the adrenal cortex and released into the systemic circulation in response to a cascade of *neuropeptides* (i.e., small chains of amino acids that act as neurotransmitters). The stress response cascade is initiated by corticotropin-releasing factor (CRF; also known as corticotropin-releasing hormone, or CRH), which is released in the cerebral cortex and hypothalamus in response to perceived stress. Recent research has established a link between a polymorphism of the gene coding for the CRF receptor and risk of depression (Liu et al., 2006). CRF in turn triggers the release of adrenocorticotropic hormone (ACTH), which is secreted by specialized neuroendocrine cells in the anterior pituitary gland and travels via systemic circulation to stimulate cortisol release from the adrenal glands. Plasma cortisol levels (i.e., the end product of the hypothalamic–pituitary–adrenocortical [HPA] axis in humans) normally follow a well-regulated diurnal rhythm: highest in the morning and lowest in the late evening. Intracellular actions of cortisol are mediated by intracellular glucocorticoid receptors, the expression of which are under genetic control (van Rossum et al., 2006) and can be up- or down-regulated by a number of factors that are relevant to depression (Neigh & Nemeroff, 2006).

A significant minority of individuals with depression show elevated cortisol levels throughout the day and blunting of the normal circadian secretory rhythm. Given the importance of glucocorticoids in systemic responses to a variety of acute stresses, including infection, hypothermia, and traumatic injury, elevated plasma cortisol levels are associated with measurably increased concentrations in virtually all body fluids, including urine, saliva, and CSF (Holsboer, 1995; Swaab, Bao, & Lucassen, 2005). In addition to elevated cortisol concentrations, increased HPA activity can be detected by several challenge paradigms, such as the dexamethasone (DEX) suppression test (DST) and the combined DST/CRH test (Holsboer, 2001). In studies of depression, various indicators of hypercortisolism are linked to older age and increased syndromal symptom severity, including psychosis and suicidal ideation, as well as a lower response to placebo and nonspecific therapeutic interventions (Thase et al., 2002).

A history of severe maltreatment or trauma during critical developmental periods can have lasting effects on regulation of the HPA axis (Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; Newport, Heim, Bonsall, Miller, & Nemeroff, 2004). In some individuals with a history of neglect or maltreatment during childhood, including those who have never developed depression, there is blunting of the axis, with reduced cortisol secretion in response to experimentally contrived stresses, such as a public speaking task (Carpenter et al., 2007). Blunted HPA response to stress is also seen in individuals with posttraumatic stress disorder (PTSD) and chronic fatigue syndrome (Bremner, 2006). Those with a history of early trauma and depression, by contrast, are more likely to show an exaggerated HPA response to stress and a state-dependent increase in plasma cortisol (Bremner, 2006; Holsboer, 2001).

The third set of pivotal findings emanate from various experimental paradigms that measure the activity of localized neuronal circuits within the brain, including several subregions of the prefrontal cortex and the core structures that comprise the limbic system (Thase

et al., 2002). Before it was possible to visualize subtle changes in regional cerebral activity in the living human, researchers obtained evidence of depression-related alterations in neuronal activity using all-night electroencephalographic (EEG) recordings during sleep (see Thase, 2006, for a comprehensive review). Such polysomnographic (PSG) recordings revealed a decrease of "deeper" slow-wave sleep (SWS) and an intensification in the amount and intensity of rapid eye movement (REM) sleep, and provided objective documentation of the difficulties that people with depression experience falling asleep and remaining asleep. Although neither of these alterations is pathognomonic to depression, the combination was shown to be relatively specific and of direct pathophysiological relevance. Because waking EEGs generally did not reveal characteristic alterations in depression, sleep appeared to unmask a characteristic alteration in the electrical activity of nuclei in the brain under the control of 5-HT and NE (Thase, Frank, & Kupfer, 1985). The PSG abnormalities associated with depression were somewhat more prevalent than was hypercortisolemia, but were nevertheless also age-dependent and more commonly observed among people with more severe, recurrent depressions (Thase et al., 2002).

More recently, studies of alterations of neuronal circuitry in depression have utilized neuroimaging strategies, including PET and fMRI scans, to measure both the structural integrity and functional activity (i.e., metabolic activity and regional blood flow at rest and in response to experimental challenges) (Drevets, 2000; Mayberg, 2003). Results of these studies, reviewed later in this chapter, have underscored the heterogeneity of depression and yielded evidence of several prototypical abnormalities, including increased activity of the amygdala, decreased activity of the dorsolateral prefrontal cortex (DLPFC), and reduced hippocampal volume (see also Davidson et al., Chapter 10, this volume).

ABNORMALITIES OF MONOAMINERGIC SYSTEMS

Noradrenergic Systems

Almost all of the NE cell bodies in the brain are located in a single nucleus, the locus ceruleus (LC), which is located in the rostral brainstem. Noradrenergic neurons project from the LC to the thalamus, hypothalamus, limbic system, basal ganglia, and cerebral cortex (see Figure 9.1) (Kandel, Schwartz, & Jessell, 1991; Kingsley, 2000). Such diffuse ascending projections reflect the role of NE in initiating and maintaining arousal in the brainstem, limbic system, and cerebral cortex, and as a modulator of other neural systems. Noradrenergic projections to the amygdala and hippocampus have been implicated in behavioral sensitization to stress (Ferry, Roozendaal, & McGaugh, 1999), and stimulation of noradrenergic fibers in the medial forebrain bundle enhances attention and increases levels of goal-directed or reward-seeking behavior (Aston-Jones, Rajkowski, & Cohen, 1999).

Noradrenergic neurotransmission plays an essential role in the experience of stress. Perception of novel or threatening stimuli is relayed from the cerebral cortex to the LC via the thalamus and hypothalamus, and from the periphery via the nucleus prepositus hypoglossi. These inputs can provoke an almost immediate increase in NE activity. Thus, cognitive processes affecting perception can amplify or dampen NE cellular responses to internal or external stimuli. In addition, activation from fibers projecting from the nucleus paragigantocellularis (probably using a small, excitatory neurotransmitter, e.g., glutamate), and release of CRH can "turn on" the LC (Nestler, Alreja, & Aghajanian, 1999). The peripheral component of stress response to stress is transmitted from the LC via the sympathoadrenal pathway to the endochromafin cells in the medulla of the adrenal glands, which in turn release

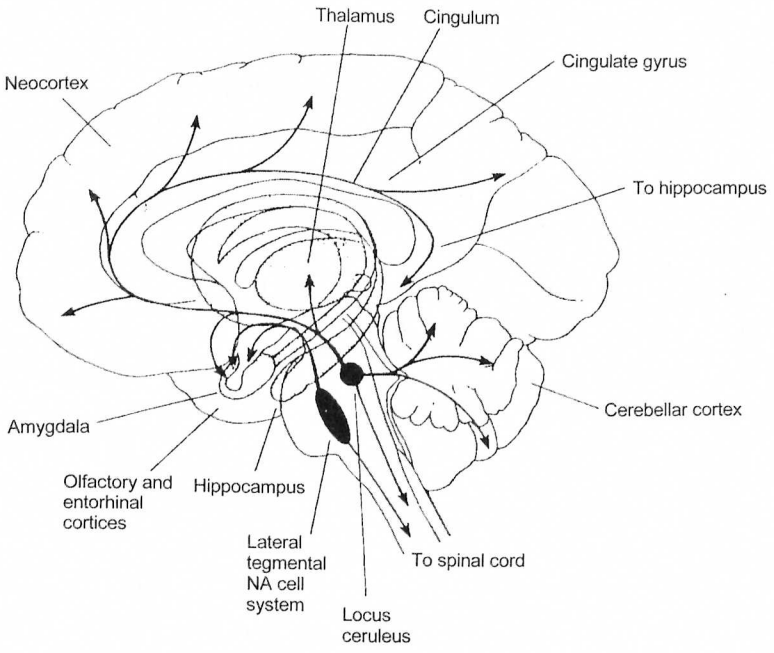

FIGURE 9.1. A lateral view of the brain demonstrates the course of the major noradrenergic pathways emanating from the locus ceruleus and from the lateral brainstem tegmentum. From Kandel, Schwartz, and Jessell (1991). Copyright 1991 by Appleton & Lange. Reprinted by permission.

NE into systemic circulation. Thus, the principal effectors of peripheral stress response, NE and cortisol, are released from glands that are located only a few centimeters apart, deep in the abdomen. The peripherally arousing effects of the sympathoadrenal response are largely mediated by cells expressing the α_1 and ß-type of NE receptors.

The activity of NE neurons is regulated in part by the autoinhibitory effects of α_2 receptors. Neuronal release of NE almost immediately begins to decrease the sensitivity of LC neurons to repeated firing. α_2 receptors also are located on serotoninergic cell bodies, and stimulation of these *heteroceptors* activates nearby (colocalized) inhibitory 5-HT neurons. A sustained increase in LC firing (i.e., a normal response to persistent stress) also causes the number of α_1 and ß-receptors to decrease, a process known as *down-regulation* or *desensitization*. Together, these four actions (i.e., α_2 autoinhibition, α_1 and ß-receptor down-regulation, and activation of adjacent inhibitory 5-HT neurons) constitute a homeostatic counterregulatory force that dampens an excessive response to a transient threat. If, however, the stress is sustained or unresolvable, intracellular stores of NE may become depleted when demand begins to exceed synthetic capacity. When this occurs, there is diminished inhibitory α_2 and 5-HT input to the LC. Thus, homeostasis of NE neurotransmission may become dysregulated, resulting in increased firing of the LC but inefficient signal transduction. Over time, the net effect is that ascending central NE neurotransmission decreases (which probably causes reduced urinary excretion of MHPG in depressed patients with psychomotor retardation), although the output of the adrenal medulla may remain high (which may explain the observation of high levels of NE and its metabolites in some severely depressed patients).

The consequences of sustained stress on NE systems in animal studies include decreased exploratory and consummatory behavior, as illustrated in studies using the learned helpless-

ness paradigm (Maier & Seligman, 1976; Maier & Watkins, 2005). Learned helplessness should not be thought of as strictly analogous to human depression: Cognitive constructs such as entrapment, powerlessness, hopelessness, and guilt distinguish depression in humans from the behavioral states experienced by rodents and dogs in learned helplessness experiments (Gilbert, 1992). Nevertheless, the changes in NE activity observed in learned helplessness experiments do parallel those associated with other animal models of depression and are associated with other neurobiological correlates of depression, including elevated glucocorticoid activity, reduced 5-HT activity, and alterations in gene transcription factors (Berton et al., 2007; Maier & Watkins, 2005; Weiss & Kilts, 1998). Moreover, recognition of the mediators of individual differences in development of helplessness—both inherited and acquired—has opened new avenues for research (Berton et al., 2007; Krishnan et al., 2007).

Despite the continued relevance of NE neurotransmission as a reliable target for medications that exert antidepressant effects, studies in the 1990s indicated that it is unlikely that dysfunction of NE systems has a primary role in the etiology of depression (Anand et al., 2000; Ressler & Nemeroff, 1999). Nevertheless, several polymorphisms associated with either synthesis of NE or its signal transduction may be associated with excessive responses to stress, which may in turn increase the risk of depression during vulnerable periods (Jabbi et al., 2007; Shelton, 2007). Altered NE response to stress may likewise play a role as a modulator of other implicated factors in depression, including both pathological processes, such as the proinflammatory cytokines (Szelényi & Vizi, 2007), and processes that promote neuronal resilience, such as those mediated by brain-derived neurotropic factor (Chen, Nguyen, Pike, & Russo-Neustadt, 2007).

The therapeutic relevance of NE is supported by several converging lines of evidence. First, antidepressants that selectively block neuronal reuptake of NE have overall clinical efficacy that is roughly comparable to that of the selective serotonin reuptake inhibitors (SSRIs) (Nutt et al., 2007; Papakostas, Nelson, Kasper, & Möller, 2007). Second, the specific additive therapeutic effect of enhancing NE is also suggested by the modest yet reproducible advantage of the so-called *dual-reuptake inhibitors* (i.e., medications that inhibit reuptake of both 5-HT and NE) versus SSRIs in meta-analyses of controlled clinical trials (Nemeroff et al., 2008; Papakostas, Thase, Fava, Nelson, & Shelton, 2007; Thase et al., 2007). Third, studies of the physiological effects of selective NE reuptake inhibitors (NRIs) have documented normalization of a variety of functional disturbances associated with depression, including pineal secretion of melatonin and blood pressure responses to changes in posture (Golden, Markey, Risby, Cowdry, & Potter, 1988; Ressler & Nemeroff, 1999). Fourth, inhibition of the synthetic enzyme tyrosine hydroxylase via administration of α-methylparatyrosine, an analogue of the NE precursor tyrosine, rapidly reverses the effects of NRIs but not of SSRIs (Delgado, 2004). Together, these data indicate that NE plays an important neuromodulatory role in the activity of antidepressant medications.

Serotoninergic Systems

Most of the serotonin (5-HT) in the brain is synthesized in clusters of cell bodies known as the dorsal raphé nuclei, located in the pons. From the dorsal brainstem, these 5-HT neurons project to the cerebral cortex, hypothalamus, thalamus, basal ganglia, septum, and hippocampus (see Figure 9.2) (Kandel et al., 1991; Kingsley, 2000). Serotonin pathways are largely colocalized with NE pathways and generally have tonic and inhibitory effects that counterbalance NE activity. For example, much evidence indicates that 5-HT input to the

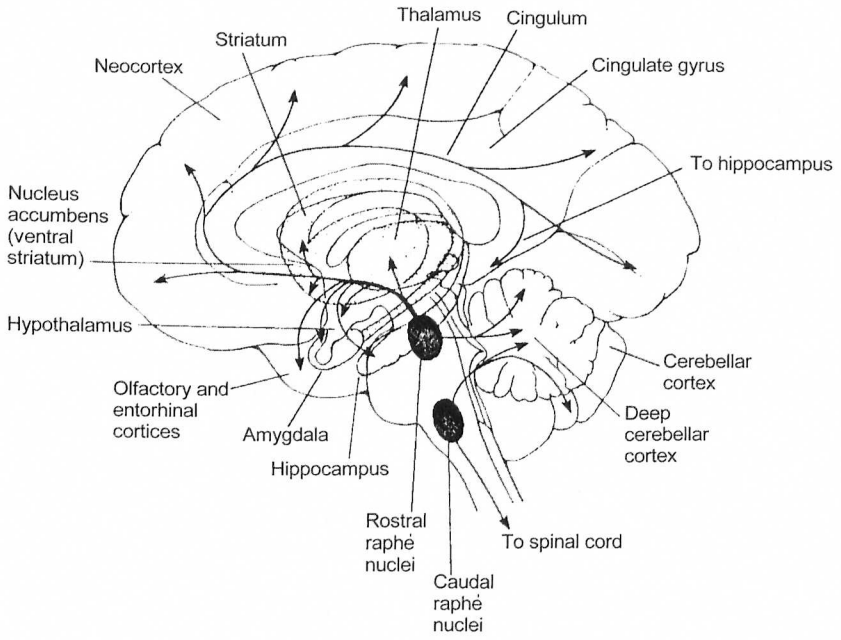

FIGURE 9.2. A lateral view of the brain demonstrates the course of the major serotoninergic pathways. Although the raphé nuclei form a fairly continuous collection of cell groups throughout the brainstem, they are graphically illustrated here as two groups, one rostral and one caudal. From Kandel, Schwartz, and Jessell (1991). Copyright 1991 by Appleton & Lange. Reprinted by permission.

thalamus is an important facilitator of appetite (Kingsley, 2000). Serotoninergic neurons projecting to the suprachiasmatic nucleus (SCN) of the anterior hypothalamus help to regulate circadian rhythms (e.g., sleep–wake cycles, body temperature, and HPA axis function) (Bunney & Bunney, 2000; Duncan, 1996). An intact 5-HT system also is needed to modulate the 90-minute infraradian cycle of alternating periods of REM and non-REM sleep (Duncan, 1996).

There are at least 15 types of serotonin receptors in the mammalian brain, each of which is under genetic control. Two of these receptors, 5-HT_{1A} and 5-HT_{2A}, have been of greatest relevance to the pathophysiology of depression and/or the mechanism of antidepressant action (Mann et al., 2001), although research on some of the more recently identified receptors, such as the 5-HT_4 and 5-HT_7, is in its infancy. All 5-HT neurons express membrane-bound transporters (5-HTT), which permit the uptake of 5-HT from the synaptic cleft. The activity of many antidepressants is initiated by blocking this transporter, including, of course, the most widely used antidepressants in contemporary clinical practice, the SSRIs. As I discuss later in this chapter, identification of a functional polymorphism in the promoter region of the gene that codes for the 5-HTT has opened multiple new lines of research and helps to explain individual differences in response to stress and antidepressant medications.

An intact basal or tonic level of 5-HT neurotransmission is necessary for both affiliative social behaviors (Insel & Winslow, 1998) and the expression of goal-directed motor and consummatory behaviors primarily mediated by NE and DA. In experimental paradigms, defeat reliably lowers basal 5-HT tone across essentially all vertebrates studied and, in the

wild, primates with lower levels of tonic 5-HT neurotransmission (as measured by CSF 5-HIAA levels) are more impulsive, aggressive, and generally have lower rankings on social dominance hierarchies than do animals with higher basal levels of 5-HT "tone" (Higley, Mehlman, Higley, et al., 1996; Higley, Mehlman, Poland, et al., 1996). Conversely, a rise in social dominance is accompanied by an increase in CSF 5-HIAA (Mehlman et al., 1995), and treatment with SSRIs decreases impulsive aggression (Fairbanks, Melega, Jorgensen, Kaplan, & McGuire, 2001). There is ample documentation of parallel associations in humans and low 5-HIAA is associated with suicide and other violent behaviors (Mann et al., 2001).

The tonic level of 5-HT neurotransmission in primates is relatively stable, with a slight seasonal variation (i.e., higher levels in the summer than in the fall) (Zajicek et al., 2000). Central serotoninergic tone is partly under genetic control (Higley, Mehlman, Poland, et al., 1996), with heritability at least partly determined by a polymorphism in the promoter region of the gene that codes for 5-HT-T. In primates, animals manifesting at least one copy of the short (S) allele, which is less functional (i.e., less transporter is synthesized, resulting in reduced uptake capability), show greater behavioral dysfunction and more exaggerated responses to stress than do animals who have two copies of the more common long (L) form of the allele (Barr et al., 2003, 2004; Shannon et al., 2005).

Humans show a similar polymorphism of 5-HTT, with the recent identification of a third variant (a less functional variant of the L form) (Firk & Markus, 2007; Levinson, 2006). Studies of the association of these polymorphisms and vulnerability to depression have yielded relatively consistent evidence of gene × environment interactions. A relation among the S allele of the serotonin transporter, stress, and increased risk of depression and suicidal ideation was first reported by Caspi and colleagues (2003) and subsequently widely (albeit not universally) replicated (e.g., see Jacobs et al., 2006; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005). Importantly, individuals with one or two copies of the S allele are not at increased risk of depression per se, but are at increased risk of depression when exposed to life stress (Firk & Markus, 2007; Levinson, 2006). Such heightened vulnerability to stress is apparent at several levels, including increased limbic blood flow (Hariri et al., 2002) or cortisol secretion (Gotlib, Joorman, Minor, & Hallmayer, 2007) in response to experimentally induced threat, elevated levels of trait-like neuroticism (Jacobs et al., 2006) or dysfunctional attitudes (Hayden et al., 2008), and use of less active coping strategies (Wilhelm et al., 2007). That this inherited vulnerability is typically manifest early in life is indirectly reflected by the results of Baune and colleagues (in press), who found that the melancholic form of depression—which typically has a later age of onset—is disproportionately associated with L alleles for the serotonin transporter. Although results of individual studies are not fully consistent, a recent meta-analysis of 15 studies found a significant association between the S allele and a lower likelihood of response or remission (Serretti, Kato, De Ronchi, & Kinoshita, 2007; see also Levinson, Chapter 8, this volume).

Reduced numbers of 5-HT uptake transporters also have been demonstrated in blood platelets (Maes & Meltzer, 1995) in the brains of depressed individuals who committed suicide (Lin & Tsai, 2004; Mann et al., 2001), and by *in vivo* receptor imaging in depressed patients (Parsey et al., 2006). This reduction in 5-HTT capacity appears to be linked directly to inheritance of the S allele of 5-HTT (Li & He, 2007; Wasserman et al., 2007).

Available evidence from studies using receptor imaging techniques suggests that dysfunction of 5-HT_{1A} receptors is clearly implicated in depression (Drevets et al., 2007). Although this abnormality could be an artifact of exposure to antidepressant medication, it has recently been demonstrated in a study of treatment-naive individuals (Hirvonen et al.,

2007). Down-regulation of 5-HT_{1A} receptors is a consequence of exposure to chronic stress, however, which—in the absence of a heritable risk factor—is the most likely explanation (López et al., 1999; Maier & Watkins, 2005). Nevertheless, an allelic variation of the 5-HT_{1A} receptor has recently been reported to be associated with risk of depression during interferon therapy (Kraus et al., 2007), so the potential contribution of a heritable vulnerability cannot be discounted.

The integrity of 5-HT neurotransmission also can be transiently compromised by dietary manipulation, specifically, by eliminating the precursor tryptophan (one of the essential amino acids) from the food source. Complete disruption of 5-HT synthesis has little immediate impact on mood in studies of healthy individuals, but it does impact more subtle aspects of cognitive–affective processing, such as enhanced anticipation of punishment (Cools, Robinson, & Sahakian, in press) and reduction of the normal attentional bias to positive emotionally valenced stimuli (Roiser et al., in press). In studies of depressed people, a brief period of tryptophan depletion does not worsen untreated depression, but it does significantly increases depressive symptoms in some unmedicated people with remitted depressive episodes (e.g., see Neumeister et al., 2006). Neumeister and colleagues (2006) also found that response to tryptophan depletion differs significantly between remitted depressed individuals and controls as a function of genetic vulnerability. Within the group of remitted depressed people, tryptophan depletion had stronger effects in individuals with at least one copy of the L allele of the 5-HTT, whereas within normal controls, only those who had two copies of the S polymorphism showed an increase in depressive symptoms.

Among patients treated for depression, tryptophan depletion can reverse acute response overnight in about 50 to 60% of people treated with SSRI antidepressants (Delgado, 2004; Delgado et al., 1991; Moore et al., 2000). Tryptophan depletion does not reverse response to placebo (Delgado, 2004). The lack of effect of tryptophan depletion on the improvement of patients treated with NRIs (Delgado, 2004), repetitive transcranial magnetic stimulation (O'Reardon et al., 2006), and cognitive therapy (O'Reardon et al., 2004) also points to the specificity of this mechanism.

Dopaminergic Systems

There are four principal DA pathways in the brain (see Figure 9.3) (Kandel et al., 1991; Kingsley, 2000). The tuberoinfundibular system projects from cell bodies in the hypothalamus to the pituitary and inhibits secretion of the hormone prolactin. The nigrostriatral system, which helps to regulate psychomotor activity, originates from cell bodies in the substantia nigra and projects to the basal ganglia. The mesolimbic pathway begins with cell bodies located in the ventral tegmentum and projects to the nucleus accumbens, amygdala, hippocampus, medial dorsal nucleus of the thalamus, and cingulate gyrus. The mesolimbic DA pathway modulates emotional expression and goal-directed or consummatory behavior. Because down-regulation of this pathway invariably accompanies learned helplessness and social defeat identifying individual differences in susceptibility has important implications for research on depression (Krishnan et al., 2007). The mesocortical DA pathway, which projects from the ventral tegmentum orbitofrontal and prefrontal cerebral cortex, subserves motivation, initiation of goal-directed tasks, and "executive" cognitive processes. Decreased DA activity has obvious implications in the motoric, hedonic, and cognitive symptoms of depression (Nestler & Carlezon, 2006; Willner, 1995). Recently, an allelic variation in the gene coding for the enzyme catechol-O-methyl transferase (COMT)—the *Val158Met* polymorphism—was found to be associated with significant differences in the experience of pos-

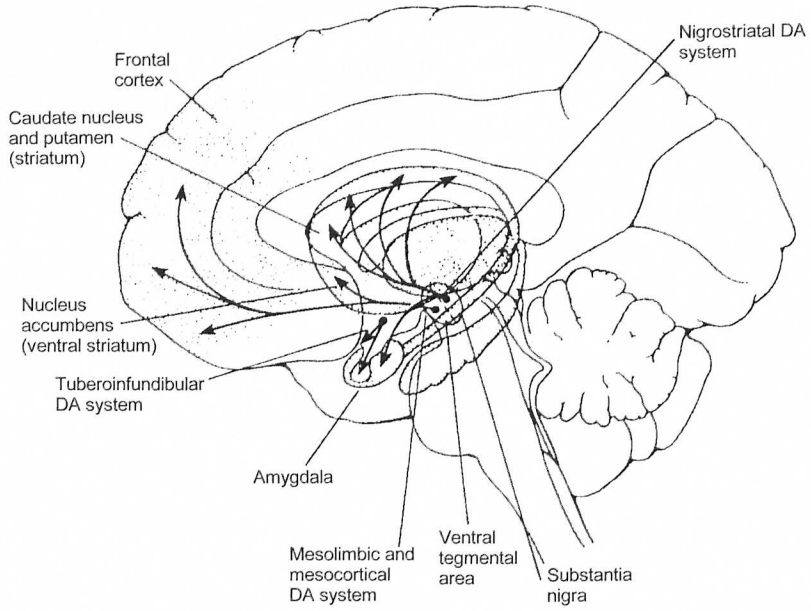

FIGURE 9.3. A lateral view of the brain demonstrates the course of the four major dopaminergic tracts. From Kandel, Schwartz, and Jessell (1991). Copyright 1991 by Appleton & Lange. Reprinted by permission.

itive affect in daily life, with individuals with one or two Met alleles experiencing significantly greater positive responses to pleasant events than those with the Val alleles (Wichers et al., in press). DA activity is also potentiated by stimulation of nicotine receptors (a subtype of receptors for acetylcholine), which may help to explain the high prevalence of tobacco consumption among depressed people (Glassman, 1993; see Freedland & Carney, Chapter 6, this volume). A selective increase in DA activity in mesocortical regions, perhaps induced by elevated cortisol levels, also may be implicated in development of hallucinations and delusions, which characterize about 10% of the most severely depressed patients (Schatzberg & Rothschild, 1992).

As with the other monoamines, chronic stress reduces DA levels and results in behavioral changes suggestive of depression (Nestler & Carlezon, 2006; Willner, 1995). For example, in an animal model of depression, chronic mild stress reduces the reinforcing effects of low concentrations of sucrose solution. Dopaminergic neurotransmission also is partly dependent on the integrity of 5-HT systems (Dremencov et al., 2004; Sasaki-Adams & Kelley, 2001), providing another example of how dysfunction in one system can provoke secondary changes in the others. Although none of the currently available antidepressants can truly be considered strongly dopaminergic, the MAOIs and perhaps bupropion and sertraline have some dopaminergic activity, and animal studies utilizing a variety of antidepressants have found that they can reverse or prevent the DA dysfunction caused by chronic stress (Cuadra, Zurito, Gioino, & Molina, 2001; Dremencov et al., 2004; Nestler & Carlezon, 2006; Willner, 1997). Among the various DA receptors that have been identified, the D_2 receptor appears to be most relevant to antidepressant activity (Gershon, Vishne, & Grunhaus, 2007). Active efforts continue to develop "triple reuptake" inhibitors, although such efforts have been difficult because of toxicity and the likelihood that a strongly dopaminergic drug would prove to be habit forming and have abuse potential.

STRESS, MONOAMINES, AND THE HPA AXIS

The foregoing discussion has emphasized the changes in monoamine function that are linked to depression, particularly in relation to the neurobiological consequences of sustained, unresolvable stress. In this section, the role of the HPA axis is considered in more detail.

Elevated HPA activity is the hallmark of mammalian stress responses, and the regulation of the axis is partly under the control of phasic NE (activating) and tonic 5-HT (inhibitory) neurotransmission. This axis has four levels of organization and modulation. In relevant areas of the cerebral cortex, the threat and contextual significance of the stressor are perceived, and the signal is relayed to the HPA. With respect to the role of the higher brain regions in HPA regulation, neurons containing the neuropeptides CRH and arginine vasopressin are diffusely located throughout the cerebral cortex, with particularly high concentrations within the thalamus, amygdala, and other components of the limbic system. Studies measuring CRH synthesis demonstrate that these brain regions "light up" immediately following exposure to stress (Holsboer, 1995; Swaab et al., 2005). Furthermore, because CRH activates the LC, which in turn further stimulates the thalamus, hypothalamus, and amygdala, sustained stress can provoke a *reverberating circuit*, or a positive feedback loop. Activating inputs from neurons are transmitted to the hypothalamus, where CRH also is released and travels systemically to the adjacent pituitary. Specialized cells in the anterior pituitary respond to CRH via release of ACTH, which travels via the bloodstream to the cortex of the adrenal glands, where glucocorticoids are released and, if the stressor is sustained, synthesis is increased. The impact of CRH stimulation is increased by simultaneous release of arginine vasopressin, which in turn is intensified during chronic stress (Swaab et al., 2005).

The cellular effects of glucocorticoids are triggered by intracellular glucocorticoid receptors (GRs), which migrate between the cell membrane and cell nuclei (Holsboer, 2000; Swaab et al., 2005). Thus, cortisol can rapidly modulate changes in the activity of a number of genes. Cortisol is the principal glucocorticoid hormone of humans. Once cortisol release is stimulated by ACTH, it is released into the circulation and exerts a large number of physiological actions on various end organs, including anti-inflammatory effects on immune function and insulin–antagonist effects on glucose and lipid metabolism. Overall, these acute changes promote short-term survival in response to overwhelming or life-threatening circumstances. Such benefits are time-limited, however, and negative compensatory (allostatic) changes begin to accumulate if cortisol levels remain elevated for prolonged periods (McEwen, 2000). Such allostatic changes include increased risks of hypertension, obesity, heart disease, osteoporosis, and autoimmune diseases, all of which appear to be increased in people with mood disorders (Evans et al., 2005).

The HPA axis, like the NE and 5-HT components of stress response, is regulated by a redundant, multilevel system of inhibitory control. This type of negative feedback inhibition occurs at all levels of the axis, including the hippocampus, hypothalamus, pituitary, and adrenal cortex. As acute stresses pass or resolve, the elevated plasma cortisol levels of healthy humans normalize within a matter of minutes or hours.

Sustained hypercortisolism thus can result from increased CRH drive (from the hypothalamus or cerebral cortex), increased secretion of ACTH (e.g., by a pituitary tumor), unrestrained noradrenergic stimulation from the LC, and/or the failure of one or more mechanisms of feedback inhibition (Holsboer, 1995; Swaab et al., 2005). There is evidence that sustained hypercortisolism can impair the integrity of HPA feedback inhibition (Bremner,

1999; Sapolsky, 1996). Exposure to various forms of stress early in life has been shown to compromise the regulation of HPA activity for a lifetime (Bremner, 1999; Coplan et al., 2001). In animal models of early trauma, even brief periods of maternal separation can result in longstanding changes in stress responses (Coplan et al., 2001, 2006). Fortunately, this effect can be partly mitigated by competent maternal behavior (Macri & Würbel, 2006). Stress in later life appears to accelerate the slow decline in the integrity of HPA axis regulation that normally accompanies aging. This age-dependent change has been shown to result, in part, from death of cells containing GRs in the hippocampus (Sapolsky, 1996), coupled with a decline in neurogenesis (i.e., the process of generation of new neurons) (Bremner, 2006). Hypercortisolism may suppress neurogenesis by decreasing neuronal synthesis of brain-derived neurotropic factor (BDNF) and is thought to play a role in the reductions in the volume of several areas of the cortex associated with depression (Bremner, 2006). Importantly, treatments that effectively reduce hypercortisolism have also been shown to at least partly reverse hippocampal volume reduction in other conditions, including PTSD (Bremner, 1999) and Cushing's disease (Starkman et al., 1999). However, because reduced hippocampal volume has been shown to be partly heritable in free-ranging primates (Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001) and has been documented in patients experiencing their first lifetime depressive episode (Frodl et al., 2002), this may be a risk factor, as well as a consequence, for hypercortisolism. Consistent with this view, primates with smaller hippocampal volumes were shown to have increased cortisol responses to experimentally induced stress (Lyons, Parker, Zeitzer, Buckmaster, & Schatzberg, 2007).

Like stress itself, hypercortisolism is not unique to depression. A significant minority of people with acute schizophrenia, mania, PTSD, and other distressing mental disorders manifest one or more signs of hypercortisolism. Across mental disorders, intensity of dysphoric arousal increases the likelihood of hypercortisolism (Thase & Howland, 1995). Abnormalities of HPA regulation also commonly occur in advanced Alzheimer's disease, presumably due to acceleration of hippocampal cell death (Swaab et al., 2005). Nevertheless, dysregulation of HPA activity plays an important role in the pathophysiology of depression and may ultimately prove to be a target for novel therapeutics of severe depressive disorders (Holsboer, 2000; Nemeroff, 1998; see Gitlin, Chapter 24, this volume).

ANTIDEPRESSANTS, MONOAMINE RECEPTORS, AND INTRACELLULAR MECHANISMS

Although it was known by the mid-1960s that TCAs and MAOIs enhance NE and 5-HT neurotransmission, several puzzling discrepancies indicated that the mechanisms underlying antidepressant response were not due simply to monoamine agonist effects. For example, although increased NE or 5-HT levels were available in the synaptic cleft within hours of administration of NE or 5-HT reuptake inhibitors, antidepressant responses took weeks to emerge (Duman, Heninger, & Nestler, 1997; Shelton, 2007). By contrast, some NE agonists, as exemplified by cocaine, were shown to have rapid mood-elevating properties but no sustained antidepressant effects. The MAOIs, which increase synaptic monoamine levels by inhibiting intracellular degradation of NE, 5-HT, and DA, similarly were associated with a time course of antidepressant effects that typically lagged at least several weeks behind the biochemical effects. Subsequently, other compounds that did not have clear-cut monoamine agonist effects, such as mianserin, also were identified to be effective antidepressants.

It is now clear that the synaptic effects of antidepressant medications initiate a sequence or cascade of effects that culminate within the nuclei of serotoninergic and noradrenergic neurons, modulating the activity of specific genes (Duman, Schlesinger, Kodama, Russell, & Duman, 2007; Shelton, 2007; Warner-Schmidt & Duman, 2006). Thus, the interplay resulting from effects on monoamine reuptake transporters and changes in the "signal" of cellular electrical activity is transduced into a series of intracellular reactions of second- and third-messengers that activate or inhibit the activity of selected genes. The pathway of action of antidepressant medication initiates an effect at 5-HT or NE receptors, whether by diffusely increasing the availability of monoamines at the synapse (i.e., the MAOIs), selectively blockading reuptake of serotonin (SSRIs), norepinephrine (NRIs; e.g., desipramine or reboxetine) or both (the SNRIs venlafaxine and duloxetine) selectively at specific receptor subtypes (e.g., the 5-HT_2 blocking antidepressants trazodone, nefazodone, mianserin, and mirtazapine). Receptor binding activates membrane-bound guanine nucleotide-binding (G) proteins and enzymes such as phospholipase C (PLC), protein kinase C, and adenlylate cyclase (AC) (Shelton, 2007). These enzymes catalyze the formation of the so-called "second messengers" (which actually are at least the third step in the sequence), such as cyclic adenomonophosphate (cAMP) and diacylglycerol. The second messengers, in turn, activate intracellular enzymes, protein kinases A and C (PKA and PKC, respectively), which phosphorylate the gene transcription factor CREB (cAMP response element binding protein). CREB appears to be the first common step shared by antidepressants that selectively modulate NE or 5-HT neurotransmission (Shelton, 2007).

Phosphorylated CREB regulates the activity of a number of genes related to stress responses, including the genes that code for CRH, GRs, BDNF, and TRKB, which is the intracellular receptor for BDNF (Duman et al., 2007; Shelton, 2007). As noted earlier, BDNF is receiving increased attention, because it has been shown to reverse or inhibit stress-induced apoptosis, it is necessary for neurogenesis, and it plays a key role in neuroplasticity (Pittenger & Duman, 2008; Warner-Schmidt & Duman, 2006). BDNF levels are significantly decreased by a variety of stressors and increased by a variety of antidepressant interventions (Martinowich & Lu, 2008; Pittenger & Duman, 2008). Importantly, whereas BDNF promotes stress resilience in brain regions such as the hippocampus, it reduces appetitive and exploratory behavior in mesolimbic regions and plays an important role in mediating behavioral responses to social defeat (Berton et al., 2006; Krishnan et al., 2007). Levels of BDNF have been shown to be reduced in the plasma of depressed people (Aydemir et al., 2006; Huang, Lee & Liu, 2009). This abnormality appears to be reversed by effective antidepressant treatment (Aydemir et al., 2006; Huang et al., 2007; Martinowich & Lu, 2008; Yoshimura et al., 2007).

OTHER NEUROTRANSMITTER DISTURBANCES

Neuron fibers containing acetylcholine (ACH) are distributed diffusely throughout the cerebral cortex and interact extensively with monoamine and glucocorticoid systems (Kingsley, 2000). At the most general level, ACH neurons have alerting or activating acute effects on brain systems, as reflected by increased release of ACTH and cortisol, increased nocturnal awakenings, and increased firing of LC neurons (Janowsky & Overstreet, 1995). The two principal subtypes of ACH receptors are called *nicotinic* and *muscarinic* receptors. Although muscarinic receptors have received the most attention, the interaction between DA and nicotinic neurotransmission also is significant (Glassman, 1993; Stolerman & Reavill, 1989).

It has long been known that drugs with agonist and antagonist effects on ACH have opposing effects on depressive symptoms (Janowsky & Overstreet, 1995). Behavioral changes following administration of an ACH agonist include lethargy, anergia, and psychomotor retardation in normal subjects and, among patients, exacerbation of depression, as well as weak and transient antimanic effects (Janowsky & Overstreet, 1995).

There is evidence from studies of animals and humans that heightened muscarinic ACH receptor sensitivity can induce some of the neurobiological changes associated with depression (Janowsky & Overstreet, 1995). For example, a mice strain bred to be supersensitive to cholinergic effects develops learned helplessness quickly when exposed to inescapable stress (Overstreet, 1993). Similarly, some remitted patients with recurrent mood disorders, as well as their never-ill first-degree relatives, manifest a trait-like supersensitivity to cholinergic agonists (Sitaram, Dubé, Keshavan, Davies, & Reynal, 1987). Elevated choline levels in depression likewise have been detected by *in vivo* studies utilizing magnetic resonance spectroscopy, particularly in basal ganglia regions (Yildiz-Yesiloglu & Ankerst, 2006). A specific gene accounting for such heightened activity has not yet been confirmed, although a polymorphism of the type 2 muscarinic receptor has been implicated (Wang et al., 2004). A state of cholinergic supersensitivity also can be induced by attenuating adrenergic activity (Schittecatte et al., 1992). Interest in the therapeutic potential of cholinergic antagonists has recently been reactivated by the work of Furey and Drevets (2006), who found that intravenous doses of scopalomine bromide have robust and relatively sustained antidepressant effects.

Gamma-aminobutyric acid (GABA) has inhibitory effects on NE and DA pathways. GABA receptors are densely localized in the thalamus and ascending mesocortical and mesolimbic systems (Kingsley, 2000; Paul, 1995). GABA is released in a calcium (Ca^{+2})-dependent fashion from interneurons in the cortex, brainstem, and spinal cord, and dampens the activity of excitatory neural circuits. Through this mechanism, inhibitory GABA-ergic neurons help to mediate the expression of the behaviors associated with learned helplessness (Berton et al., 2007). There are two principal subtypes of GABA receptors, referred to as A and B (Paul, 1995). Benzodiazepines and barbiturates attach to $GABA_A$ receptors, which serve to "gate" the control of membrane chloride (Cl^-) ion channels. This results in localized hyperpolarization of neurons, which decreases their responsivity to excitatory neurotransmitters. $GABA_B$ receptors are indirectly coupled to membrane potassium (K^+) channels via a G-protein and have uncertain clinical relevance (Kingsley, 2000; Paul, 1995).

Chronic stress can reduce or deplete GABA levels in these regions of the brain, perhaps reflecting, yet again, an example of an excessive demand outstripping the capacity for synthesis (Weiss & Kilts, 1998). Reduction of GABA levels in people with depressive disorders has been observed in plasma and CSF specimens (Petty, 1995), in postmortem tissues of individuals who completed suicide (Rajkowska et al., 2007; Sequeria et al., 2007), and in studies using proton magnetic resonance spectroscopy *in vivo* (Hasler et al., 2007). Reductions of cortical volume in regions of the prefrontal cortex and hippocamupus, at least in part, appear to be the result of reductions in GABA-ergic interneurons in the surrounding glia (Rajkowska et al., 2007). Although sustained normalization of GABA function has not yet been demonstrated in longitudinal studies of clinical populations, some evidence does suggest normal GABA function among recently remitted individuals (Hasler et al., 2005).

The excitatory amino acid glutamate is one of the most widely distributed neurotransmitters in the CNS (Kingsley, 2000). There are two broad types of glutamate receptors: the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor and the *N*-methyl-D-aspartate (NMDA) receptor. AMPA receptors are ionotropic (i.e., cation channels) transmembrane receptors that mediate fast synaptic transmission in the brain. AMPA recep-

tors (AMPARs) are essential for development of long-term potentiation (LTP) of neurons, one of the best-studied forms of neuroplasticity. AMPARs comprise four types of glutamate subunits, designated as Glu_{R1}, Glu_{R2}, Glu_{R3}, and Glu_{R4}, which combine to form tetramers. Most AMPARs are either homotetramers (i.e., four units of Glu_{R1} or Glu_{R4}) or symmetric combinations of two units of Glu_{R2} and a second dimer that comprises Glu_{R1}, Glu_{R3}, or Glu_{R4}; each subunit has a binding site for glutamate. The ion channel opens when at least two sites are occupied. Most AMPARs in the brain include Glu_{R2} subunits, which are impermeable to calcium, hence helping to guard against neurotoxicity.

The NMDA receptor is an ionotropic receptor for glutamate (and, to a lesser extent, aspartate); activation of these receptors opens nonselective ion channels that allow sodium and calcium influx and potassium efflux. It is the calcium influx that results in the critical role that NMDA receptors play in both synaptic plasticity and neurotoxicity. NMDA receptors comprise heterodimers formed by NR_1 and NR_2 subunits; multiple receptor isoforms are characterized by distinct patterns of distribution within the brain and unique functional properties. Each receptor has three regions, which constitute the extracellular, membrane, and intracellular domains. The extracellular domain includes NR_1 subunits that bind to glycine and NR_2 subunits that bind to glutamate. The membrane domain includes the channel pores, which are highly permeable to calcium and are subject to a voltage-dependent magnesium block. The intracellular domain contain residues that are modifiable by protein kinases and protein phosphatases.

The potential relevance of drugs that activate AMPARs or block NMDA receptors to a range of CNS disorders is increasingly recognized (Bleakman, Alt, & Witkin, 2007; Palucha & Pilc, 2005; Pittenger, Sanacora, & Krystal, 2007). Importantly, intracellular accumulation of glutamate has neurotoxic effects, particularly for glial cells (Rajkowska & Miguel-Hidalgo, 2007), and neurons and glial cells in the hippocampus and amygdala have high concentrations of NMDA receptors (Mathew et al., 2001; Rajkowska & Miguel-Hidalgo, 2007). With respect to antidepressant effects, the recent findings of Zarate and colleagues (2006) are of considerable interest: They confirmed that infusions of the NMDA antagonist ketamine have rapid, robust, and relatively sustained therapeutic effects in a small, but well-controlled, study of patients with refractory depressive disorders. Although both the mode of administration (intravenous) and the propensity for psychomimetic effects necessarily delimit the therapeutic utility of ketamine per se, extensive research directed at identifying other compounds without these drawbacks is ongoing in a number of laboratories.

ABNORMALITIES OF HORMONAL REGULATORY SYSTEMS

HPA Axis Dysregulation

As briefly noted earlier, increased secretion of plasma cortisol is one of the best documented biological correlates of depression. Beyond simply measuring cortisol concentrations in various body fluids at one point in time, more detailed investigations have collected integrated measures of HPA axis activity across a number of hours or cortisol responses to various provocative challenges, including the much-maligned DST or the more refined combined DST/CRH infusion test.

That hypercortisolemia in depression is heavily severity-dependent is readily apparent in differences in prevalence: Whereas only 20–40% of depressed outpatients show elevated cortisol concentrations in plasma or urine specimens, up to 60–80% of depressed inpatients manifest increased cortisol concentrations. Consistent with this observation, hypercortisol-

emia is at least twice as likely in studies of patients with melancholic (i.e., endogenous) or psychotic forms of depression as in studies of individuals with less severe forms of major depressive disorder (Holsboer, 1995; Thase & Howland, 1995).

Hypercortisolism has several therapeutic implications. Patients with increased HPA activity appear to be less responsive to placebo (Ribeiro, Tandon, Grunhaus, & Greden, 1993) or psychotherapy (Thase et al., 1996) than are individuals with more normal HPA activity, and persistent hypercortisolemia—despite apparently effective antidepressant therapy—is associated with an increased risk of subsequent relapse (Holsboer, 1995; Ribeiro et al., 1993). Development of safer, more selective CRH antagonists was once considered by some to be the area of greatest therapeutic promise (Holsboer, 2000; Nemeroff, 1998), although slow progress in this area has somewhat dampened enthusiasm.

Thyroid Axis Dysregulation

Thyroid gland dysfunction has long been known to be associated with increased risk for depression (Fountoulakis et al., 2006; Thase et al., 1985). In addition to *hypothyroidism* (a clinical diagnosis based on low basal levels of thyroid hormone and characteristic symptoms, e.g., fatigue, weight gain, cold intolerance, and dry skin), there are less clear-cut cases of "subclinical" hypothyroidism in which basal thyroid hormone levels are still within normal limits but there is evidence of diminished response to the hypothalamic (thyrotropin-releasing hormone; TRH) or pituitary (thyroid-stimulating hormone; TSH) neuropeptides that drive the thyroid axis (Fountoulakis et al., 2006; Thase et al., 1985). It is important to note, however, that relatively few people seeking treatment for depression have frank hypothyroidism, and only a small percentage may be considered to have subclinical hypothyroidism (Fountoulakis et al., 2006; Thase et al., 1985). Normal thyroid function is nevertheless essential for the integrity of CNS processes such as energy metabolism (Bauer et al., 2003) and neurogenesis (Montero-Pedrazuela et al., 2006); moreover, there is evidence that even subtle reductions in the activity of the thyroid axis may be associated with reduced responsiveness to antidepressants or greater risk of relapse (Cole et al., 2002; Joffe & Marriott, 2000). Because of these characteristics, augmentation of an ineffective antidepressant medication with thyroid hormone is a reasonably well-tolerated strategy that benefits a minority of patients with treatment-resistant depression (Nierenberg et al., 2006) and may actually speed antidepressant response in treatment-naive, depressed patients (Cooper-Kazaz et al., 2007).

A significant minority of depressed patients with otherwise normal basal thyroid hormone levels—up to 40% in studies of depressed inpatients—manifest a blunted TSH response to a test dose of TRH (Mason, Garbutt, & Prange, 1995). This altered response, which paradoxically would normally be suggestive of hyperthyroidism, does not rapidly reverse with effective treatment and is predictive of increased risk of relapse (Kirkegaard & Faber, 1998). Within the context of normal basal levels of thyroid hormones, a blunted TSH response to TRH is indicative of down-regulation of thyrotropin responsiveness as a consequence of increased extrahypothalamic "drive" on the thyroid axis (Holsboer, 1995). Like the increased drive on the HPA axis, this appears to be part of the brain's homeostatic response to sustained dysphoric activation.

Growth Hormone and Somatostatin

Growth hormone (GH) is secreted by cells in the anterior pituitary in response to the hypothalamic neuropeptide growth hormone–releasing factor (GHRF), as well as noradrenergic

stimulation via α_2 receptor stimulation of NE (Holsboer, 1995). GH secretion is principally inhibited by the neuropeptides somatostatin and CRH. Significant concentrations of somatostatin are found in the amygdala, hippocampus, nucleus accumbens, prefrontal cortex, and LC (Plotsky, Owens, & Nemeroff, 1995). In addition to its inhibitory effects on GH release, somatostatin dampens the effects of other activating neuropeptides, including CRH. GH secretion normally follows a 24-hour circadian rhythm, with highest levels between 2300 and 0200 hours. Thus, the nocturnal rise in GH secretion is normally synchronized with the first few hours of sleep, especially during the first non-REM sleep period, in concert with the greatest amount of deep, slow-wave sleep (SWS; Steiger, 2007). The most consistent alteration of GH associated with depression is blunted release in response to a variety of agents with noradrenergic agonist effects, including various antidepressants and the selective α_2 agonist clonidine (Holsboer, 1995; Thase & Howland, 1995). Blunted GH release has been documented in childhood-onset depression (Dahl et al., 2000) and appears to be both trait-like (Coplan et al., 2000) and most pronounced among depressed people with diminished SWS (Steiger, 2007).

Prolactin

Prolactin, which is involved in regulation of reproductive functions, such as nursing and menstruation, is released from the pituitary in response to stimulation of 5-HT_{1A} receptors and inhibited by stimulation of D_2 receptors (Kingsley, 2000). Although most studies of basal prolactin secretion have not detected abnormalities in depressed patients, blunted prolactin response to various 5-HT agonists has been found in some, but not all, studies (Maes & Meltzer, 1995; Mann et al., 2001). Of note, blunted prolactin responsivity is less likely to be found in studies of premenopausal women, which suggests that higher levels of circulating estrogen have a facilitative effect on 5-HT_{1A} neurotransmission (Parry & Haynes, 2000). Elevated prolactin levels, on the other hand, may be a consequence of therapy with most of the older antipsychotic medications, as well as several of the newer generation of antipsychotics, such as risperidone.

ALTERATIONS OF SLEEP NEUROPHYSIOLOGY

The neurochemical processes mediating sleep are fairly well characterized (Steiger, 2007). The propensity to sleep follows a circadian rhythm marked by a nocturnal rise in the pineal hormone melatonin and by low levels of ACTH and cortisol. Melatonin is released from the pineal gland following the onset of darkness in response to ß-adrenergic stimulation. The sleep–wake circadian rhythm is "paced" by the suprachiasmatic nucleus of the hypothalamus. There is also a 90-minute infradian cycle oscillating between REM and non-REM sleep; this cycle is normally suppressed during wakefulness. The desynchronization of EEG rhythms following sleep onset partly reflects decreased activity of the LC and increased inhibitory activity of GABA-ergic and 5-HT neurons; the latter effect appears to be mediated by 5-HT_2 receptors (Horne, 1992; Steiger, 2007). Beyond facilitating sleep onset, 5-HT neurons tonically inhibit the onset of REM sleep; this effect appears to be mediated by 5-HT_{1A} receptors. Near the end of each 90-minute REM–non-REM cycle, 5-HT neurons cease firing, which "releases" the pontine cholinergic neurons that initiate REMs. The depth of sleep also is facilitated by certain neuropeptides, including ghrelin, galanin, and neuropeptide Y, and disrupted by others, including CRH and somatostatin (Steiger, 2007).

As noted earlier, a significant proportion of people with depression manifest reduced SWS and an early onset of the first period of REM (also referred to as *reduced REM latency*; Benca, Obermeyer, Thisted, & Gillin, 1992; Thase, 2006). Reduced REM latency and decreased SWS are significantly correlated, in large part because 30 to 40 minutes of SWS during the first non-REM sleep period normally inhibits the onset of the first REM period. SWS propensity is partly under genetic control, and consistent with trait-like behavior, reduced SWS often persists following clinical recovery (Kupfer & Ehlers, 1989; Thase, Fasiczka, Berman, Simons, & Reynolds, 1998). Although both of these changes in sleep electrophysiology are observed with aging, depression appears to accelerate this process by a decade or more (Thase, 2006). The findings are more evident among men and postmenopausal women than among premenopausal women, perhaps reflecting the "sparing" effects of estrogen on deep sleep (Thase, 2006).

Compared to age-matched healthy controls, people with depression also experience an increase in nocturnal awakenings and a decrease in total sleep time. Whereas reduced SWS appears to be state-independent, sleep continuity disturbances associated with depression are to some extent correlated with symptom severity. Unlike normal aging, depression is also associated with an increase in the frequency and amplitude of REM sleep (Thase, 2006). Such changes in the phasic activity of REM sleep, which are quantified as measures of REM intensity or density, are greatest during the first several REM periods. Increased *phasic* REM sleep typically co-occurs with other state-dependent biological abnormalities, including hypercortisolemia (Kupfer & Ehlers, 1989; Thase & Howland, 1995). Increased phasic REM sleep is more pronounced in recurrent depression than in a single lifetime episode—both during depressive episodes (Thase et al., 1995) and following remission (Jindal et al., 2002)—and is one component of a profile of sleep disturbances associated with poorer response to psychotherapy (Thase et al., 1996, 1997). Although linked to severity and at least partly reversible with effective treatment, increased indices of phasic REM sleep also appear to identify people at high risk for depressive disorder (Modell, Ising, Holsboer, & Lauer, 2005).

Antidepressants have variable effects on measures of sleep efficiency that are largely linked to secondary properties, such as antihistaminergic effects (Sharpley & Cowen, 1995; Thase, 2006). Potent monoamine oxidase reuptake inhibitors that are not sedating tend to be relatively sleep-neutral, with some tendency for increased nocturnal awakenings to be slightly offset by improvements in subject complaints of insomnia (Thase, 2006). Drugs that block 5-HT_{2C} receptors, including mirtazapine and agomelatine, may have an advantage over SSRIs and SNRIs in terms of improvements in sleep efficiency (Thase, 2006; Zupancic & Guilleminault, 2006), although there is no evidence to indicate a stronger overall antidepressant effect.

Most antidepressants, including the SSRIs, SNRIs, TCAs, and MAOIs, rapidly delay the onset of REM sleep and suppress phasic REM sleep (Sharpley & Cowen, 1995; Thase, 2006). Pharmacological REM suppression is mediated by stimulation of 5-HT_{1A} receptors, as well as by less well-characterized effects of NE neurotransmission. Because nonpharmacological deprivation of REM sleep (implemented by EEG-monitored awakenings) also was shown to have at least transient antidepressant effects, for a time researchers postulated that REM suppression was a necessary action of antidepressant therapies (e.g., Thase & Kupfer, 1987). However, REM suppression is only weakly correlated with antidepressant efficacy (Thase & Kupfer, 1987) and neither a number of novel antidepressant medications, including bupropion (Nofzinger et al., 1995), nefazodone (Rush et al., 1998), and agomelatine (Zupancic & Guilleminault, 2006), nor psychosocial interventions, such as cognitive ther-

apy (Thase et al., 1998), significantly suppress REM sleep. Together, these findings indicate that REM suppression is neither a necessary nor sufficient element of antidepressant therapy.

DEPRESSION AND CIRCADIAN RHYTHMS

Sleep disturbances, increased cortisol secretion, blunted nocturnal GH secretion, and elevated nocturnal body temperature all reflect abnormalities of circadian biological rhythms, with severe depression possibly representing an abnormal phase advancement of circadian rhythms (Wirz-Justice, 1995). Researchers also noted that depressed people have disruptions of the social zeitgebers ("time givers" such as mealtimes, periods of companionship, and exercise) that help to entrain circadian rhythms (Ehlers, Frank, & Kupfer, 1988). A review of later studies of depression suggested that the alterations in associated circadian rhythms were better viewed as a disorganization of functions than as a phase advance (Thase et al., 2002). Thus, the state of dysphoric activation that characterized more severe depressions—whether mediated by increased CRH and cortisol levels or decreased inhibitory neurotransmission from 5-HT or GABA pathways—may simply "overpower" the more subtle regulation of circadian rhythms. There is, however, evidence of a circadian phase delay in the subset of patients that experiences recurrent winter depression (Lewy et al., 2007) that is responsive to manipulations of the photoperiod via bright white, morning light or dawn stimulation (Avery et al., 2001; Lewy et al., 2007).

IMMUNOLOGICAL DISTURBANCES

Depressive disorders are associated with several immunological abnormalities, including decreased lymphocyte proliferation in response to mitogens and other forms of impaired cellular immunity (Irwin & Miller, 2007; Petito, Repetto, & Hartemink, 2001; Raison, Capuron, & Miller, 2006). These lymphocytes and macrophages produce proinflammatory peptides, such as C-reactive protein (CRP), and cytokines, such the interleukins (ILs), which in turn interact with neuromodulators, such as BDNF and CRH (Irwin & Miller, 2007; Petito et al., 2001; Raison et al., 2006). Although depression is not invariably associated with alterations in immune response, the number of studies reporting positive associations is too great to discount, and this relationship is at least likely to contribute to the increased risk of inflammatory diseases, including arthritis, allergy, and atherosclerosis, associated with depression (Glassman & Miller, 2007). Studies of the behavioral and neurochemical effects associated with interferon are illustrative (Felger et al., 2007; Lotrich, Rabinovitz, Gironda, & Pollock, 2007; Wichers et al., 2007). Of note, the risk of depression during interferon therapy may be linked to an allelic variation in the gene for the 5-HT_{1A} receptor (Kraus et al., 2007) and is attenuated by pretreatment with antidepressants (Raison et al., 2007).

CEREBRAL METABOLIC STUDIES IN DEPRESSIVE DISORDERS

The activity of neuronal circuitry may be visualized in the living brain via PET or fMRI scans. In studies utilizing PET to measure cerebral glucose utilization (because glucose is the primary source of energy for neurons, it is an excellent marker of neuronal activity), experi-

mentally provoked dysphoria has been shown to increase cerebral blood flow (CBF) to the thalamus, medial prefrontal cortex, and amygdala in healthy individuals (Mayberg, 2003), with deactivation of the DLPFC observed in some studies (see Freed & Mann, 2007). The most widely replicated PET finding associated with clinical depression is reduced glucose utilization in the anterior cortical structures, including DLPFC (Drevets, 2000; Mayberg, 2003). Reductions in DLPFC activity have also been documented in studies using fMRI (Harvey et al., 2005; Siegle, Thompson, Carter, Steinhauser, & Thase, 2007). Because this relative hypofrontality has been observed in unipolar, bipolar, and secondary depressions (Baxter et al., 1989), it appears to reflect a common final pathway for diverse depressive states. Frontal hypometabolism has been shown to be reversible following switches from depression into mania in bipolar depression (Ketter et al., 1994), as well as in response to both psychotherapy and pharmacotherapy (Brody et al., 2001; Goldapple et al., 2004; Martin, Martin, Rai, Richardson, & Royall, 2001).

In addition to a global reduction of anterior cerebral metabolism, increased glucose metabolism has been observed in several limbic regions, most prominently in the amydala (Drevets, 2000). The strongest evidence of limbic hypermetabolism is found in studies of patients with a family history of severe, recurrent depression, hypercortisolemia, or PSG abnormalities (Drevets, 2000; Nofzinger et al., 2000). Among this high-risk group, limbic hypermetabolism is suppressed by effective pharmacotherapy, but appears to reemerge when patients are restudied off medication (Drevets, 2000) or following 5-HT depletion (Bremner et al., 1997; Neumeister et al., 2006). As initially reported by Hariri and colleagues (2002) in healthy control subjects manifesting the "at-risk" S allele of the 5-HTT, amygdalar hypermetabolism appears to be the emotional "amplifier" that helps to distort the signal of relatively minor stressors in vulnerable people. Interestingly, abnormalities of prefrontal and limbic systems appear to be unrelated (i.e., having one does not increase the likelihood of manifesting the other), at least in mildly to moderately depressed patients (Siegle et al., 2007); thus, they may represent distinctly different targets for intervention (Siegle, Carter, & Thase, 2006). There is some evidence that that cognitive-behavioral therapy and antidepressant medication result in different patterns of changes in CBF, with psychotherapy showing a greater impact on anterior cortical structures, and medication having a greater effect on subcortical structures, including the amygdala (Goldapple et al., 2004; Kennedy et al., 2007).

SUMMARY

Major depressive disorder is a heterogeneous clinical entity; not surprisingly, therefore, it has been associated with a wide range of neurobiological disturbances. The characteristics that have been shown to be at least partly state-dependent—including elevated peripheral levels of NE metabolites, increased phasic REM sleep, poor sleep maintenance, hypercortisolism, impaired cellular immunity, decreased DLPFC activity, and increased activity in the amygdala and related paralimbic regions—tend to coaggregate among more severely symptomatic patients, particularly older patients who have experienced recurrent depressive episodes; this constellation partly maps onto the classic clinical prototype of endogenous depression or melancholia.

The trait-like neurobiological characteristics of depression—including low 5-HIAA, decreased SWS, reduced REM latency, blunted nocturnal growth hormone response, increased responsivity to stress, and possibly reduced hippocampal volume—are associated with an

early age of onset and a more chronic illness course, as well as greater heritability. In people manifesting these traits, symptom expression early in the course of the illness may be shaped by the developmental trajectory of functional inhibitory response systems (i.e., 5-HT and GABA), resulting in symptoms that are atypical of melancholia, such as overeating and oversleeping. Given that estrogen enhances these inhibitory responses, it is not surprising that reverse-neurovegetative features are most common among depressed premenopausal women.

Nevertheless, it is also true that responses to stress, aging, and neurobiological sequelae of recurrent depression are almost inextricably interwoven, and many individuals experience a shift in the predominant symptoms and response to treatment over time. During youth and young adult life, the onset of the first depressive episode is almost invariably associated with significant stress (Kendler, Karkowski, & Prescott, 1999); this relation is strongest in individuals with a history of increased genetic risk (Caspi et al., 2003; Kendler et al., 2005). This association unravels in midlife for individuals with a history of recurrent depressive episodes (Kendler, Thornton, & Gardner, 2001), however, in concert with the increasing prevalence of state-dependent neurobiological abnormalities. Relevant later-life diseases of the brain that impair brain function—including cerebrovascular disease and Alzheimer's disease—subsequently heighten vulnerability to depression, even among those with low heritable risk.

FUTURE DIRECTIONS

Although many aspects of the neurobiology of depression remain only partly understood—and some findings that appear quite promising in 2008 are likely to be false leads—there has been tremendous progress in the 6 years since publication of the first edition of this *Handbook*. The major developments include further clarification of the associations between both stress responses and antidepressant actions to intracellular processes, including those relevant to a large number of heritable factors that may be associated with individual differences in the vulnerability to, clinical characteristics of, and therapeutic responses in depression. Using messenger RNA as an indicator of gene activity, it is now possible to determine which genes are "turned on" or "turned off" by particular stressors or interventions. To the extent that gene products can be measured reliably in plasma or CSF or be "tagged" with radionucleotides that permit visualization of gene activity in the living brain, these techniques are increasingly relevant in clinical research. Even when *in vivo* measurement is not possible, research applications using relevant animal models of depression and postmortem brain tissue are providing important new data.

Following completion of mapping the human genome, it has become possible to study the relations among various polymorphisms for gene products relevant to neurotransmission (i.e., genes that code for proteins involved in the metabolism and signal transduction of monoamines, excitatory amino acids, and glucocorticoids) and familial risk for mood disorders. The explosion of research that followed recognition of the link between the less functional S allele of the serotonin transporter and increased response to stress in terms of limbic activation (Hariri et al., 2002) and risk of depression (Caspi et al., 2003) is illustrative of but one of many possible links to vulnerability. Research targeting heritable resilience factors (i.e., gene products that are shown to reduce the impact of other risk factors) holds comparable promise (Southwick, Vythilingam, & Charney, 2005). Not only will the next decade of research help to clarify further the complex biopsychosocial pathways of illness transmission, but it may also lead to identification of potential new mechanisms for inter-

vention. The ultimate goal of such research will be development of treatments that have enduring or truly curative effects.

Finally, changes in relevant regions of the brain in response to various pharmacological or psychological mood induction paradigms, and in response to various information-processing tasks, have now been extensively studied. These studies reveal both similarities and differences between people suffering from depression and the sadness or distress experienced by healthy controls. Consistent with other lines of evidence, the overall pattern of these results supports a continuum of model of psychopathology, spanning the range across "normal" dysphoria, grief, and minor depression, and the mild, moderate, and most severe forms of major depressive episodes. Dysphoric affect is associated with activation of the amygdala and related limbic structures, with a progressive reduction of the DLPFC that is associated with increasing syndromal severity. The next generation of research will focus on the reversibility of structural changes associated with depression, such as increased amygdalar volume and decreased hippocampal size, as well as on development of more efficient and powerful interventions that directly target these abnormalities. Until such strategies are available, early recognition of depression, vigorous treatment leading to complete remission of symptoms, and subsequent prophylaxis to minimize the risk of relapse or recurrence represent the best means available to mental health professionals to lessen the functional and neurobiological consequences of this ubiquitous illness.

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