Neuroscience Basis of Clinical Depression: Implications for Future Antidepressant Drug Development

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This column reviews progress in our understanding of the neuroanatomy, pathophysiology, and genetics underlying clinical depression. Such understanding is fundamental to the ability to rationally identify the neural regulatory processes involved and develop drugs specifically targeted to those processes. The goal of the column is to help clinicians better conceptualize the nature of depressive illness and its treatment and educate their patients about these issues. *(Journal of Psychiatric Practice* **2009;15:125–132**)

KEY WORDS: clinical depression, neuroscience, antidepressant drug development, brain imaging, hippocampus, amygdala, genetics

As regular readers of this column know, three variables determine the effect of any drug in any patient as expressed in Equation 1 (p. 126). The pharmacology of the drug is determined by its ability to bind to and alter the function of one or more sites of action (i.e., regulatory proteins). In doing so, the drug is capable of altering human physiology and thus producing both its good and adverse effects.

As regular readers also know, one can either start with the effects of a drug and search for the mechanisms that mediate its effects, or one can start with a site of action and design a drug to produce specific effects. Pharmacology began with the first paradigm: observe an effect and search for the underlying mechanism. That was true for all of the first classes of psychiatric medications: antidepressants, antipsychotics, anxiolytics, and mood stabilizers. The reason psychiatric pharmacology began in this way was that not enough was initially known about the physiology underlying psychiatric illness to use the other paradigm. However, that has begun to change over the last decade. This column reviews the progress that has been made in understanding the neuroanatomy and neurophysiology underlying clinical depression. Such understanding is fundamental to the ability to rationally identify new neural regulatory processes for drug development, enabling researchers to use the second paradigm mentioned above.

The goal of this column is not to provide an exhaustive explanation of the nuances of this area of research, but rather to provide an adequate framework to help clinicians conceptualize the nature of depressive illness and its treatment. With this knowledge, clinicians can in turn educate their patients to help them better understand their illness and improve their active participation in treatment, in much the same manner as clinicians provide such information to patients with diabetes, hypertension, or other general medical conditions.

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This column is adapted with permission from Chapter 6 in: Preskorn SH. Outpatient management of depression, 3rd ed. Caddo, OK: Professional Communications; 2009:63–75.

Disclosure statement: Dr. Preskorn, as chief executive officer of the Clinical Research Institute, Wichita, KS, and, in many cases, as principal investigator, has received grants from the following entities: AstraZeneca, Biovail, Boehringer-Ingelhaim, Bristol-Myers Squibb, Comentis, Cyberonics, Eisai, EnViVo, GlaxoSmith-Kline, Merck, Memory, Organon, Otsuka, Pfizer, Sepracor, Somerset, Wyeth, and the National Institute of Mental Health. He has served as a consultant, on the advisory board, and/or as a speaker for the following: Biovail, Bristol-Myers Squibb, Comentis, Covedien, Cyberonics, Eli Lilly, EnViVo, Evotec, Fabre-Kramer, Jazz, Memory, Organon, Pfizer, Somerset, Transcept, and Wyeth.

Equation 1 *© Preskorn 2007*

Clinical response	=	Affinity for and intrinsic activity at the site of action (pharmacodynamics)	X	Drug concentration at site of action (pharmacokinetics) (ADME)	X	Underlying biology of patient (GADE)
				• **A**bsorption • **D**istribution • **M**etabolism • **E**limination		• **G**enetics • **A**ge • **D**isease (diagnosis) • **E**nvironment (internal)

Anatomy and Physiology

Significant progress in this area has resulted from advances in basic neuroscience and brain-imaging research. This work has identified thalamic, pallidal (i.e., globus pallidus), striatal (i.e., caudate nucleus and putamen), and cortical areas of the brain that are important in assigning affective meaning in man.[1,2] As shown in Figure 1, there is a parallel between this affective circuit and circuits that process visual, spatial, and motor meaning in the brain. This parallel may help clinicians understand these brain circuits and conceptualize the pathophysiology of clinician depression and other affective illnesses (e.g., bipolar disorder).

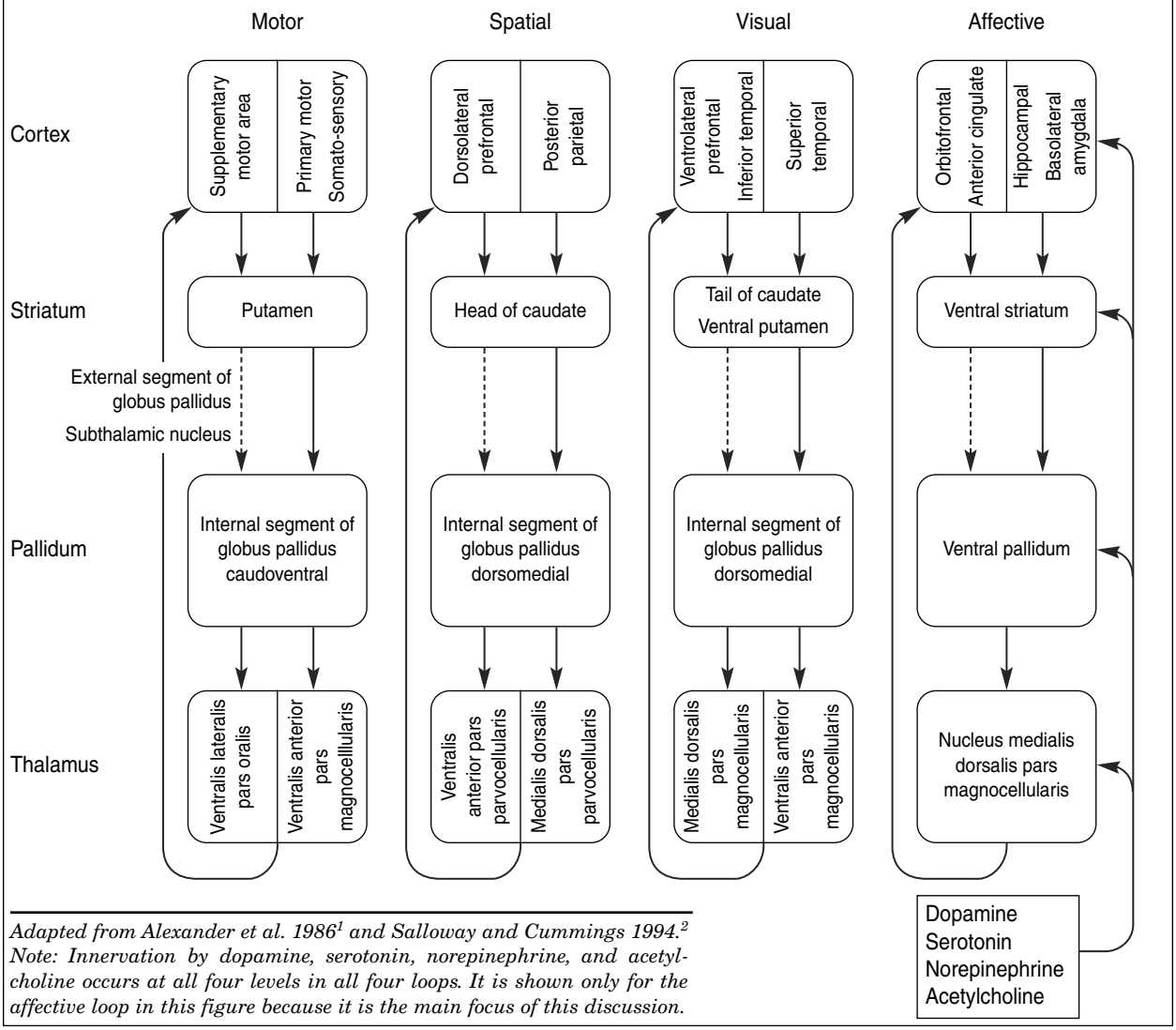
As can be seen in Figure 1, these regions are innervated by serotonin, norepinephrine, dopamine, and acetylcholine neurons. This fact provides a framework for understanding why drugs that affect these monoaminergic neurons, such as antidepressants, can modify affective processing and hence treat affective illness.

Both functional and structural disturbances in specific brain regions have been imaged in patients with clinical depression. These principal regions and their functions include:

- Ventromedial prefrontal cortex (VMPFC)
  - Modulates pain and aggression, and sexual and eating behaviors
  - Regulates autonomic and neuroendocrine response to stressors or threats[3–5]
- Lateral orbital prefrontal cortex (LOPFC)
  - Activity is increased in depression, obsessive-compulsive disorder, posttraumatic stress disorder, and panic disorder
  - Corrects and inhibits maladaptive, preservative, and emotional responses[5,6]
- Dorsolateral prefrontal cortex (DLPFC)
  - Involved in cognitive control, solving complex tasks, and manipulation of information in working memory
  - Hypoactivity of DLPFC in depression has been associated with neuropsychological manifestations of depression.[5,7]
- Amygdala
  - Regulates cortical arousal and neuroendocrine responses to aversive, surprising, and ambiguous stimuli
  - Has a role in emotional learning and memory
  - Degree of amygdala activation correlates with degree of depression
  - Implicated in tendency to ruminate on negative memories[5,8,9]
- Hippocampus
  - Plays a role in episodic, contextual learning and memory
  - Is rich in corticosteroid receptors, particularly in rodents but less so in primates
  - Is involved in a feedback loop that regulates hypothalamic-pituitary-adrenal axis function
  - Hippocampal dysfunction may be responsible for inappropriate emotional responses.[5,10–12]

Functional brain disturbances have primarily been assessed by measurements of cerebral blood flow, which in turn are closely correlated with energy metabolism, and also by direct measurement of regional glucose metabolism.[13–15] Brain regions in which such functional disturbances have been identified include the orbitofrontal cortex, ventromedial and ventrolateral prefrontal cortex, pregenual and subgenual portions of the anterior cingulate cortex, posterior cingulate cortex, parahippocampal cortex, superior temporal cortex, ventromedial striatum, amygdala, and medial thalamus (Figure 2). Metabolic rates in these regions are either positively or negatively correlated with the degree of depressive symptomatology in patients, as measured by instruments such as the Hamilton Rating Scale for Depression.[16] Changes in such scales are routinely used to measure symptomatic improvement in the depressive illness produced by antidepressant therapy. Effective treat-

Figure 1. Cortical-striatal-pallidal-thalamic circuits: Motor, spatial, visual, and affective loops



Adapted from Alexander et al. 1986[1] and Salloway and Cummings 1994.[2]
Note: Innervation by dopamine, serotonin, norepinephrine, and acetylcholine occurs at all four levels in all four loops. It is shown only for the affective loop in this figure because it is the main focus of this discussion.

ment with antidepressants of several different biogenic amine types produces changes in metabolic activity in virtually all of these brain regions.

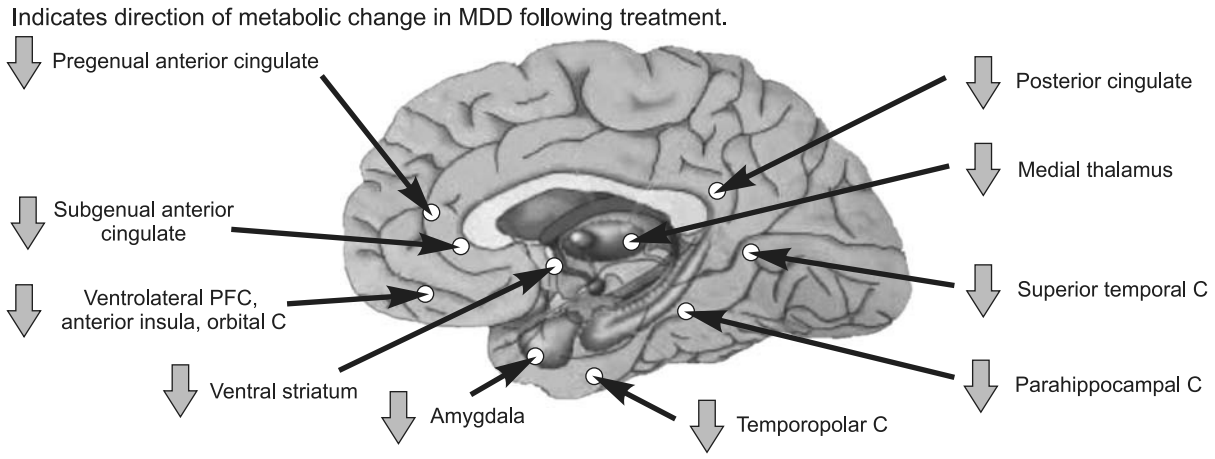
Reductions in volume using magnetic resonance imaging and/or cellular reductions as assessed by postmortem microscopic studies of the brains of depressed patients have been documented in some of these same regions.[17]

Depressive episodes can also result from multiple microvascular lesions in these frontal and striatal areas and from frontal lobe infarcts or tumors, particularly on the left side.[14] That is consistent with the well recognized fact that the same type of disturbance in brain function can be caused by different pathogenetic mechanisms, as long as they affect the same brain regions. However, the course of the disturbance and its response to treatment will differ as a function of the underlying pathogenetic mechanisms rather than the brain region affected.

Hippocampus

Disturbances in the hippocampus and amygdala deserve special comment because they may be central to the pathophysiology of clinical depression, contributing to both the cognitive impairment and

Figure 2. Metabolic changes associated with effective antidepressant drug treatment



Courtesy of Wayne Drevets, as modified from Drevets WC. Brain structural abnormalities in mood disorders. In: Zorumski CF, Rubin EH, eds. Psychopathology in the genome and neuroscience era. Washington, DC: American Psychiatric Publishing; 2005: 119–52. Scientific evidence from Drevets et al. 2002[13] and 2004.[14]

emotional and neuroendocrine dysregulation observed in major depressive disorder.[18] Such dysfunction may result from a combination of excessive excitatory input from the VMPFC and increased levels of glucocorticoids leading to a "toxic" effect on the hippocampus consistent with the observation of the hippocampal atrophy in patients with clinical depression.[19,20]

This hypothesis ties together the observations that antidepressants can work via effects on serotonin (5-HT), norepinephrine (NE), and glutamate mechanisms, as discussed in the last column.[21] 5-HT and NE neurons in the brain stem, particularly the dorsal raphe and locus coeruleus, respectively, influence the balance between excitatory (glutamatergic) and inhibitory (gamma-aminobutyric acid [GABA]ergic) activity in the prefrontal cortex and limbic system. In turn, excitatory (glutamatergic) neurons from the prefrontal cortex have feedback regulatory influence on the firing of NE and 5-HT neurons in the locus coeruleus (LC-NE) and dorsal raphe nuclei, respectively.

Amygdala

Amygdala lesions in animals impair acquisition of fear conditioning, the recognition of fear in facial expression, and the development of innate fear in dominance hierarchies.[22–25] In man, volumetric reductions in the amygdala are associated with a more severe course of depressive illness, including psychotic forms of the illness, and with familial forms of the illness. In animals, stimulation of the amygdala produces fear, anxiety, sadness, cortisol secretion, defense response, and sympathetic arousal. In man, such stimulation also produces emotional memories. In both animals and man, amygdala neuronal activity increases during exposure to aversive stimuli or stimuli predicting aversive outcome and to emotionally arousing or socially salient sensory stimuli.

The amygdala, in concert with the VMPFC, may be a link between the long recognized functional disturbances in the hypothalamic-pituitary axis (HPA) in depressive illnesses, repeated stress, and the possible role of glutamate in some forms of depressive illness.[26] The administration of hydrocortisone in a dose-dependent fashion increases amygdala responses to the presentation of sad faces in normal controls. The infusion of corticotrophin-releasing hormone agonists and corticosterone into the amygdala and repeated stress have been postulated to produce hyperexcitability of amygdala neurons, an activated state of glutamate N-methyl D-aspartate (NMDA)-receptor function, and increased "silent" NMDA-receptor expression. This functional anatomy could be relevant to the rapid and robust antidepressant effects seen with NMDA antagonists,[27–29] (studies

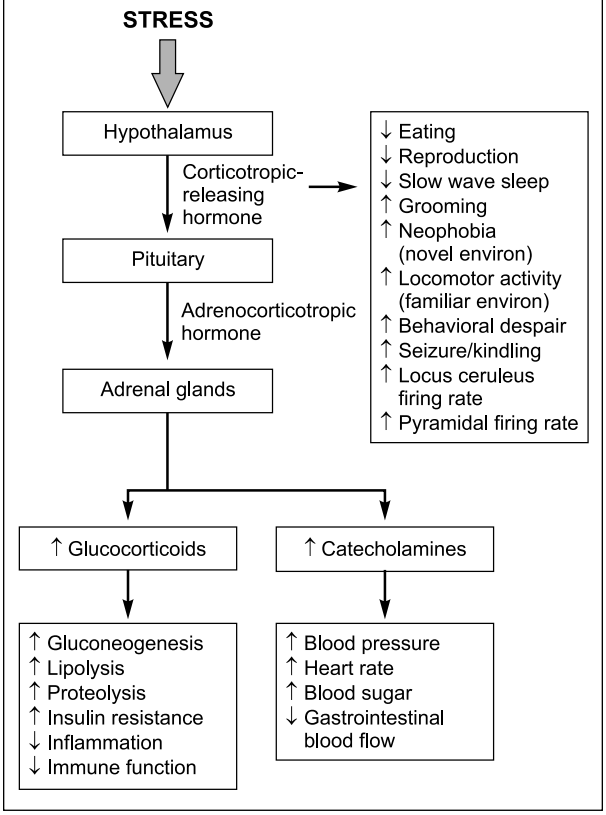
involving these agents will be discussed in detail in a future column).

HPA Dysfunction and Systemic Consequences of Clinical Depression

The overactivity of the HPA axis as a result of clinical depression and/or repeated bouts of severe and persistent stress can produce the systemic consequences of clinical depression and account in part for the increased medical comorbidity and disability associated with depression, as illustrated in Figure 3,[30–32] as follows:

1. The hypothalamus stimulates the pituitary gland to release excessive adrenocorticotropic hormone (ACTH), which in turn continuously drives the adrenal gland to release excessive amounts of catecholamines and cortisol.
2. Increased systemic levels of catecholamines, in turn, can cause hypertension, leading to both congestive heart failure and myocardial ischemia with diminished heart rate variability, which can contribute to ventricular arrhythmias and sudden death.
3. Increased systemic levels of catecholamines can also cause platelet activation and increases in cytokines and interleukins, which can further contribute to hypertension and atherosclerosis.
4. Increased systemic levels of cortisol antagonize insulin and thus contribute to the development of dyslipidemia, type 2 diabetes, and obesity and can suppress the immune function leading to increases in cancer and other illnesses and increased mortality rates[30] (Figure 3).

Figure 3. Relationship between stress, the hypothalamic-pituitary axis, and systemic responses



Receptor and Genetic Findings

There is evidence of increased muscarinic (M) and reduced 5-HT1A receptor function in depression.[6] Specific polymorphisms of M-2 receptors and of the suppressor for 5-HT1A receptors are risk factors for clinical depression. Brain-imaging studies have found reduced M-2 binding in patients with bipolar but not unipolar depression[33] and reduced presynaptic and postsynaptic 5-HT1A receptor binding in the raphe and mesiotemporal cortex, respectively.[6]

Parenthetically, presynaptic 5-HT1A receptors on serotonin neurons in the raphe modulate the firing rate of serotonin neurons and the synthesis and release of serotonin. Treatment with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) results in downregulation of the 5-HT1A receptor in a time course that coincides temporally with the onset of their antidepressant activity. Buspirone and pindolol also affect this receptor, which is the theoretical basis for their use as augmentation strategies for SSRIs and SNRIs.[34]

Glucocorticoids and repeated stress inhibit the expression of the mRNA for 5-HT1A receptors while stimulation of hypothalamic 5-HT1A receptors increases ACTH.[35–37]

A variation in the promoter sequence for the serotonin transporter protein (5-HTT, also called the serotonin reuptake pump) has been identified involving either a 44-base pair insertion (5-HTT-L) or deletion (5-HTT-S). Based on functional magnetic resonance imaging studies, these genotypes have been reported to have functional significance in the amygdala.[38] They have also been reported to be asso-

ciated with differential response to two different SSRIs, fluvoxamine and paroxetine,[39,40] and to be a risk factor for experiencing a depressive episode after repeated stressful life events.[41]

The 5-HTT (i.e., serotonin reuptake pump) is the putative mechanism of action of SSRIs and one of the putative mechanisms of action of SNRIs and tertiary amine tricyclic antidepressants.[42] Through its effects on the vagus nerve, the vagus nerve stimulator, the only device currently approved by the Food and Drug Administration for treatment-refractory depression (TRD), has an impact on virtually all of the regions discussed in this section, which formed a substantive part of the basic science impetus for testing its efficacy in patients with TRD.[34]

Beyond Classic Neurotransmitters

In addition to their effects on classic neurotransmitters, particularly 5-HT and NE, antidepressants have also been found to have downstream effects on intracellular mechanisms, including brain-derived neurotrophic factor (BDNF). That may be critical to the long-term beneficial effects of maintenance treatment with antidepressants.

Neurogenesis occurs in brain areas critically implicated in the pathophysiology of clinical depression (e.g., the hippocampus).[43] BDNF is associated with production of new neurons and with their growth and development.[44] Neurotrophins modify synaptic transmission in an activity-dependent manner.[45] Both neurogenesis and BDNF production are downregulated by stress, based on studies done in animals.[46] Both are also downregulated in clinical depression based on studies done in humans.[44,47]

Table 1 summarizes neurotransmitters and other neural mechanisms that are relevant to the pathophysiology and treatment of major depression, including the relationship between depression and stressful life events.

Table 1. Neurotransmitters and other neural mechanisms of relevance to the pathophysiology and treatment of major depression

Serotonin
Norepinephrine
Dopamine
Glutamate
Acetylcholine
Corticotropin releasing factor (CRF)-adrenocorticotropic hormone (ACTH)
cyclic adenosine monophosphate (c-AMP)/brain-derived neurotrophic factor (BDNF) and neurogenesis
Histamine
Gamma-aminobutyric acid (GABA)
Neurokinins/"Substance P"

Conclusion

While the understanding of the neuroanatomy, pathophysiology, and genetics underlying clinical depression and its treatment is far from complete, great strides are being made. A gestalt is beginning to emerge that ties together the genetic predisposition to clinical depression, the effect of repeated and/or persistent stress, and how continuous antidepressant use can produce increased 5-HT and/or NE tone in the prefrontal cortex and limbic system, alterations in neural activity in the VMPFC, DLPFC, hippocampus, and amygdala, and increased activity in the DLPFC. We are also beginning to understand how these changes, in turn, are correlated with symptomatic improvement in major depressive disorder, including a decrease in sadness, anxiety, psychomotor retardation, and fatigue, and improvement in cognitive functioning, and how activation of 5-HT and/or NE input may be helpful in restoring adaptive homeostasis by modulating the balance between excitatory and inhibitory inputs in these brain areas. Such understanding holds the promise of identifying new targets for rational development of novel psychiatric medications that can more fundamentally correct the pathophysiology underlying clinical depression. The goal of such drug development will be to discover agents that have the ability to enhance neuroplasticity and neurogenesis and afford neuroprotection. The resulting agents will not simply provide symptomatic treatment of conditions such as clinical depression but instead will prevent and potentially reverse the degenerative brain changes seen in such illnesses.

For more discussion of this area of research, readers may also want to review the series of columns on

the human genome project and drug development that appeared earlier in this journal and is available on-line at www.preskorn.com.[48]

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