

# Norepinephrine Dysfunction in Depression

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The study of the noradrenergic neurotransmitter system remains one of the cornerstones of depression research. Better understanding of the action of norepinephrine and other catecholamines at the synaptic and intracellular level holds the potential for providing clues to the etiology of depression and introduces exciting possibilities for the development of novel medications for the treatment of depression. The following review of norepinephrine as it relates to depression will shed light on the current understanding of the noradrenergic system and the role for selective norepinephrine reuptake inhibitors (selective NRIs) in the treatment of depression.

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The discovery of imipramine, an effective norepinephrine antidepressant, 4 decades ago and the subsequent exposition of the catecholamine hypothesis have firmly established a role for norepinephrine (NE) in the etiology and treatment of depression.<sup>1,2</sup> It was originally thought that a simple deficiency in NE was the basis for some forms of depression. However, as our understanding of the cellular mechanisms that underlie depression has unfolded over the last decade, the role for NE has been both expanded and modified. Medications that enhance the function of the noradrenergic system are once again coming to the forefront of clinical care. This rebirth of noradrenergic agents is based not only on the increased understanding of the role of NE, but on the improved tolerability and safety profiles of the current, more selective, norepinephrine reuptake inhibitors (selective NRIs).

Recent studies have shown that a decrease in synaptic NE is associated with depressive symptoms. Other investigations have identified several adrenergic receptor subtypes and delineated their role in the modulation of presynaptic and postsynaptic neuronal function. However, it has also been recognized that alterations in noradrenergic neurotransmission alone cannot explain the etiology of

depression. Rather, abnormalities involving interactions with other neurotransmitters—e.g., serotonin (5-HT), neuropeptides, corticotropin-releasing hormone (CRH), and other hormones—may be the basis for the depressed state. Recently, the complex intracellular machinery that translates the postsynaptic effects of neurotransmitters into long-term effects on protein synthesis and genomic effects has begun to be unraveled. These breakthroughs have come about because the advanced methodology to study neurotransmitters has developed at a rapid pace. Matters as complex as the plasticity of the nervous system are beginning to be understood. Exciting new work has linked NE to the very viability of neurons in critical brain structures. These new insights have provided exciting possibilities for the development of novel medications for the treatment of depression.

## NEUROCHEMISTRY OF THE NORADRENERGIC SYSTEM

The major noradrenergic nucleus in the brain is the locus ceruleus, which is located on the floor of the fourth ventricle in the rostral pons.<sup>3</sup> Noradrenergic neurons give rise to diffuse axonal projections that innervate virtually all areas of the brain. Projections from noradrenergic neurons to the prefrontal cortex (an area involved in drive and motivation) and the hippocampus (involved in learning memory) may play a particularly important role in the type of depressive symptoms expressed.

The locus ceruleus is very sensitive to both external environmental stimuli and changes in the body's internal homeostasis. Further, output from the locus ceruleus is involved in flight-and-fight responses, regulation of levels of arousal, and control of the sleep-wake cycle. In addition, noradrenergic neurons projecting from the locus ceruleus modulate responses of the sympathetic nervous system, including pulse rate, blood pressure, and danger

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signals for the organism. Therefore, it is not surprising that abnormal activity of the noradrenergic system has been implicated in the pathophysiology of both anxiety and depression.<sup>3</sup> Locus ceruleus neurons receive a number of inputs that provide information about the state of the body's internal environment. These inputs include other neurotransmitter systems, e.g., 5-HT, opioid,  $\gamma$ -aminobutyric acid (GABA), dopamine, and glutamate. A number of peptides influence the firing rate of these locus ceruleus neurons, the most notable of which is CRH. Finally, the noradrenergic system itself provides negative feedback to the locus ceruleus neurons.<sup>3,4</sup>

The synthetic and metabolic pathway for catecholamines involves a series of enzymatic reactions (Figure 1). The rate-limiting enzyme for the synthesis of both NE and dopamine is tyrosine hydroxylase.

Receptors on noradrenergic neurons have been classified as being either  $\alpha$ - or  $\beta$ -adrenergic subtypes. Each of these subtypes has at least 2 secondary subtypes ( $\alpha_1$  and  $\alpha_2$ ;  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ ). Each of these subtypes has been cloned.<sup>5</sup> Considering the rate of discovery, it is quite likely that other forms of these receptors exist that have different functional properties and regional distribution.  $\alpha_2$ -Adrenoceptors (heteroreceptors) are also present on terminals of the serotonergic neurons in the hippocampus. Electrophysiologic studies suggest these heteroreceptors exert a tonic inhibitory influence on the firing of serotonergic neurons.<sup>6</sup>

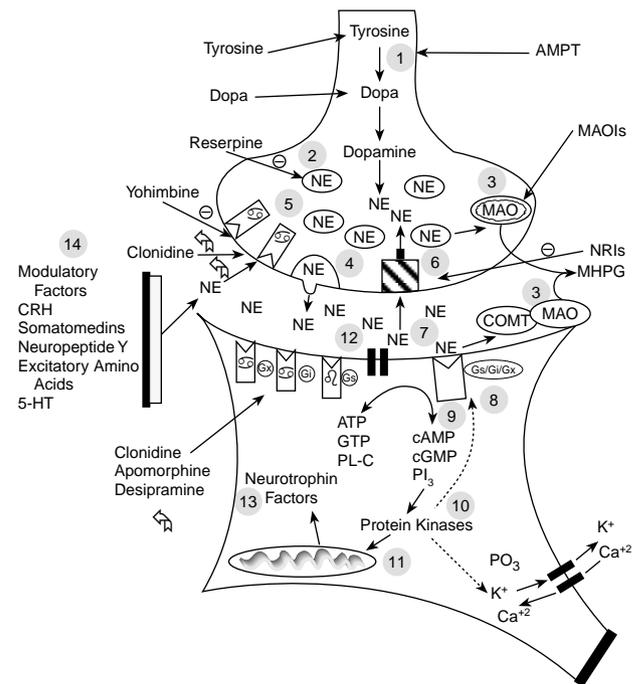
In summary, the noradrenergic system is closely related to cortical regions that are involved in mood regulation and cognitive arousal. It is also closely related to subcortical regions responsible for hormonal and somatic manifestations of mood such as the hypothalamus, pituitary, and peripheral sympathetic system.

## NOREPINEPHRINE DEFICIENCY IN DEPRESSION

The principal active metabolite of norepinephrine is 3-methoxy-4-hydroxyphenylglycol (MHPG). A consistent relationship of altered MHPG levels in cerebral spinal fluid, serum, or urine has not been found in patients with depression.<sup>7</sup> However, several studies have reported that patients with bipolar depression have lower plasma and urinary levels of both NE and MHPG compared with patients who have unipolar depression.<sup>8,9</sup> It has also been reported by several authors that the degree of bipolarity may be associated with the extent of the deficiency of NE.<sup>1,9,10</sup>

Many different parameters have been assessed in trying to uncover the basis for the link between norepinephrine and depression. Researchers have looked at ratios of both NE and epinephrine to their metabolites, total body catecholamine turnover, ratios of NE to NE plus metabolites, and epinephrine to epinephrine plus metabolites, as well as discriminant functional analysis of 24-hour urinary catecholamines and metabolites (depression [D]-type scores).

Figure 1. Role of Norepinephrine (NE) in the Etiology of Depression and Mechanism of Action of Antidepressants<sup>a</sup>



<sup>a</sup>Schematic model of a central noradrenergic neuron indicating sites that may be involved in the etiology of depression and the mechanism of antidepressant action. **1. Enzymatic synthesis:**  $\alpha$ -Methylparatyrosine (AMPT) blocks tyrosine hydroxylase, the rate-limiting enzyme for NE synthesis. **2. Storage:** Reserpine interferes with the uptake-storage mechanism of amine granules, and chronic treatment causes depletion of catecholamines. **3. Metabolism and turnover:** NE is metabolized by monoamine oxidase (MAO) presynaptically and catechol-O-methyltransferase (COMT) in the synapse; 3-methoxy-4-hydroxyphenylglycol (MHPG) is the major metabolite. **4. Release:** Amphetamine increases net release of NE. **5. Autoreceptors** are  $\alpha_2$  type. Clonidine has agonist activity and yohimbine, antagonistic activity; stimulation of autoreceptors leads to decrease in NE transmission. **6. Reuptake site:** NE has its action terminated by being taken up into the presynaptic terminal. Desipramine is a selective uptake inhibitor. **7. Postsynaptic receptors** are  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$  types; clonidine, apomorphine, and desipramine are agonists at  $\alpha_2$  receptor sites.  $\beta$ -Receptor down-regulation is one of the most consistent effects of long-term antidepressant treatment. **8. G proteins:** Coupling proteins translate the effects of postsynaptic receptor stimulation into effects on the second messenger, e.g., cyclic adenosine monophosphate (cAMP) system. **9. Second messenger system:** Consists of cAMP, cyclic guanosine monophosphate (cGMP), and the phosphatidylinositol (PI) system; production is stimulated or inhibited by G proteins and they in turn activate or inhibit protein kinases. **10. Protein kinases:** The third messenger system activates or inhibits phosphorylation of enzymes involved in protein synthesis in the neuron and can affect synthesis and distribution of receptors. **11. Genome:** Protein kinases may also act by activating the synthesis of proteins and enzymes directly from the genetic code. **12. Ion channels** are ultimately responsible for neuronal firing; they can be directly activated via the G proteins or their activity modified by the actions of protein kinases. **13. Neurotrophic factors:** Protein kinases may stimulate production of neurotrophic factors such as neurotrophin-3 (NT-3), which can increase NE transmission and increase the survival of NE neurons. **14. Modulatory factors:** A number of modulatory factors can affect NE transmission, including neuropeptides such as corticotropin-releasing hormone (CRH), somatomedin and neuropeptide Y, excitatory amino acids, e.g., glutamate, aspartate, and serotonin (5-HT). Other abbreviations: ATP = adenosine triphosphate, GTP = guanosine triphosphate, MAOI = MAO inhibitor, NRI = norepinephrine reuptake inhibitor, PL-C = phospholipase C.

These studies have shown that unipolar depressed patients have a higher excretion of catecholamines compared with control subjects or patients with bipolar depression.<sup>11</sup>

Several research groups have found that patients who have a robust response to either tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) have reduced levels of urinary MHPG.<sup>12,13</sup> In contrast, with the monoamine oxidase inhibitor (MAOI) phenelzine, responders had the same decrease in MHPG as nonresponders.<sup>14</sup> Posttreatment reductions in MHPG following the administration of imipramine have not been associated with a treatment response.<sup>14</sup> Of note is that decreases in MHPG with antidepressant treatment have been associated with an increase in NE excretion.<sup>13</sup> However, changes in the levels of catecholamine metabolites are not consistent, but vary with the duration of treatment.<sup>9</sup>

To evaluate the effects of acutely depleting catecholamines, patients with depression and healthy control subjects were given alpha-methylparatyrosine (AMPT), a tyrosine hydroxylase inhibitor, and then monitored for the emergence of symptoms. In healthy subjects, the chronic administration of AMPT induced no depressive symptoms,<sup>15</sup> whereas in bipolar depressed patients, AMPT was noted to increase the symptoms of depression.<sup>16,17</sup> However, mood changes were not observed when nonmedicated patients with depression were given an AMPT challenge.<sup>18</sup> Another study reported that medication-free euthymic subjects with a remote history of depression experienced a relapse of their depressive symptoms on administration of AMPT.<sup>19</sup>

Miller and colleagues<sup>18</sup> reported that administration of AMPT reversed the antidepressant response of NRIs but not that of SSRIs. Therefore, it appears that the specific mechanism of antidepressant action of the NRIs is to increase the level of NE.

Chronic antidepressant treatment has also been shown to affect the synthesis of NE in the brain. Tyrosine hydroxylase activity or messenger RNA (mRNA) levels are decreased by chronic treatment with most antidepressants including the SSRI fluoxetine and the MAOI phenelzine.<sup>20-22</sup> The significance of this finding is not clear, although this may be an example of a homeostatic mechanism in response to increased availability of NE in the synapse.

Suicide victims are frequently reported as having been depressed. To determine if there might be biological evidence of change in suicide victims, Ordway<sup>23</sup> examined postmortem tissue taken from the locus ceruleus of suicide victims and compared it with tissue from age-matched, natural or accidental death control subjects. The authors reported that levels of tyrosine hydroxylase and the density of  $\alpha_2$ -adrenoceptors (norepinephrine receptors) were elevated in the tissue from suicide victims compared with controls. Similar biological changes were observed in tissue from the locus ceruleus of rats that were repeatedly

exposed either to the kind of environmental stimuli that activates the locus ceruleus or to treatment with pharmacologic agents that deplete brain NE. The authors hypothesized that persons who commit suicide have experienced chronic activation of the locus ceruleus, which, in turn, results in the depletion of synaptic NE and compensatory changes in tyrosine hydroxylase levels in noradrenergic neurons.

One possible mechanism that may explain the biological changes is an increase in CRH production, which in turn leads to an increased turnover of NE in the locus ceruleus. Under such a scheme, chronically elevated levels of CRH would lead to increased NE turnover and ultimately NE depletion.<sup>24,25</sup> CRH antagonists such as alpha human corticotropin-releasing hormone could decrease this effect and prevent the emergence of depression.<sup>26</sup>

In summary, NE deficiency has been shown to be associated with depression. A deficiency in norepinephrine could arise from an intrinsic abnormality of production and release or from a secondary depletion, resulting from a chronic stimulation of the NE system (e.g., induced by chronic stress). Medications that increase NE availability such as the NRIs and MAOIs, therefore, are potentially the most effective antidepressants available for the treatment of depression.

#### NORADRENERGIC RECEPTOR DYSFUNCTION IN DEPRESSION

Besides NE deficiency, an abnormality in NE neurotransmission can also arise from changes in postsynaptic NE receptor sensitivity. Different hypotheses have been proposed along these lines.

##### Postsynaptic $\alpha_2$ Receptor Down-Regulation

Another biological change that has been observed in depressed nonmedicated patients compared with healthy controls of a similar age is an abnormal growth hormone (GH) response to the administration of clonidine.<sup>27</sup> The phenomenon has been shown to be mediated through postsynaptic  $\alpha_2$  receptors and is reported to be unaffected by antidepressant treatment.<sup>28</sup> However, a challenge with a number of different pharmacologic agents (e.g., the serotonergic agent *m*-chlorophenylpiperazine [*m*-CPP]) appears to result in abnormal GH responses.<sup>29</sup> Therefore, it may be that a blunted GH response stems from an intrinsic abnormality in the GH system in depression. Long-term antidepressant treatment with desipramine, amitriptyline, clorgyline, trazodone, or mianserin<sup>30-34</sup> does not reverse the blunted GH response to clonidine in depression; this is not the case for lithium.<sup>35</sup> Several authors have found a blunted neuroendocrine response to desipramine in depression mediated via postsynaptic  $\alpha_2$  receptors.<sup>36,37</sup> When the  $\alpha_2$  receptors on platelets of patients with depression are examined, the findings are inconsistent. Some studies

have shown an increased number and greater sensitivity of  $\alpha_2$  receptors, while others have not.<sup>38-40</sup> Recent studies of tissue from the locus ceruleus region of suicide victims have shown an increased density of  $\alpha_2$  receptors compared with controls.<sup>23</sup> A change in the density and responsivity of the  $\alpha_2$  receptors may be present in depression, a phenomenon that may be secondary to a NE deficiency.

### Presynaptic $\alpha_2$ Receptor Dysfunction

The effects of clonidine on blood pressure, pulse rate, and MHPG secretion have not been found to be consistently different between patients with depression and controls, leading most authors to the conclusion that presynaptic  $\alpha_2$  function remains intact in depression.<sup>41</sup> Studies with yohimbine, an  $\alpha_2$ -adrenergic receptor antagonist, suggest an increased sensitivity of the presynaptic  $\alpha_2$  receptors in depression. This finding contradicts the results from the clonidine challenge studies. Long-term treatment with desipramine and amitriptyline,<sup>7,27,30,42</sup> but not trazodone or mianserin,<sup>32,33</sup> decreases presynaptic  $\alpha_2$  receptor function. This decrease is likely to be secondary to a homeostatic response to an increase in synaptic NE.

### $\alpha_1$ Receptor Up-Regulation

Neurophysiologic studies have suggested that antidepressants may work by increasing postsynaptic  $\alpha_1$  adrenergic responsivity.<sup>43-46</sup> This hypothesis has not been fully explored in clinical studies.

### $\beta$ -Adrenergic Receptor Down-Regulation

Postsynaptic  $\beta$ -adrenergic receptor down-regulation is the most consistent and robust long-term effect of most antidepressant agents, including electroconvulsive therapy (ECT).<sup>42,47,48</sup> However, weak or no effects on down-regulation have been noted for mianserin, bupropion, and maprotiline.<sup>49,50</sup> Many agents that cause down-regulation of  $\beta$ -adrenergic receptors, e.g., yohimbine, are not efficacious in augmenting the effects of NRIs.<sup>51</sup> Propranolol, a  $\beta$ -adrenergic receptor antagonist, has been associated with an increased incidence of depression.<sup>52</sup> Conversely, thyroid hormone, which up-regulates  $\beta$ -receptor function, is an important augmenting agent in the treatment of depression with standard antidepressant drugs.<sup>53,54</sup> Therefore,  $\beta$ -adrenergic receptor down-regulation is considered a homeostatic response to the action of antidepressant drugs rather than their mechanism of action. Prolonged stimulation of  $\beta$ -adrenergic receptors can lead to adaptations in the intracellular signal transduction pathways leading to changes in receptor expression, phosphorylation, and/or subcellular distribution, which ultimately manifests as  $\beta$ -adrenergic receptor down-regulation.<sup>48</sup>

Down-regulation of  $\beta$ -adrenergic receptors is the most consistent effect of antidepressants seen in preclinical studies. Clinical studies also point to a down-regulation of  $\alpha_2$ -adrenergic receptors by antidepressants. However, the

down-regulation of both these receptors is more likely an adaptation to chronic antidepressant administration rather than a primary antidepressant mechanism of action.

## INTERACTION OF NOREPINEPHRINE WITH OTHER NEUROTRANSMITTERS AND NEUROPEPTIDES

Brain neurotransmitter systems such as NE, dopamine, 5-HT, and acetylcholine interact with each other and modulate each other's functions. Furthermore, each of these systems is modulated by other factors, e.g., CRH, vasopressin, somatomedins, neuropeptide Y, cytokines, excitatory amino acids and *N*-methyl *D*-aspartate (NMDA) receptor function, and brain neurotrophic factors. Therefore, any hypothesis for the pathophysiology of depression and mechanism of drug action needs to take into account the complexity of the regulation of central nervous system (CNS) function. Catecholamines undoubtedly play a central role in depression since they have been shown to be affected by other factors that have been implicated in depression.

Interaction of dopamine with NE and the catecholamines with the 5-HT system is an important area of research. Noradrenergic denervation prevents TCAs from causing sensitization of forebrain neurons to 5-HT in laboratory animals.<sup>55</sup> Lesions of the 5-HT system increase low agonist affinity  $\beta$ -adrenergic receptor density,<sup>56</sup> and NE has been shown to have an inhibitory effect on the 5-HT system through the presynaptic heteroreceptors.<sup>6</sup> Depletion of both NE and dopamine results in greater blunting of the GH response to clonidine in rats than NE depletion alone.<sup>57</sup>

CRH has been shown to acutely increase the locus ceruleus firing rate. However, effects of chronically elevated CRH (as seen in depression)<sup>58</sup> on noradrenergic neurons have not been delineated. Chronic desipramine treatment attenuates the stress-induced activation of locus ceruleus neurons mediated by CRH neurotransmission.<sup>59</sup> Desipramine treatment has been shown to reduce cerebral spinal fluid CRH concentrations.<sup>60</sup> Neuropeptide Y is another peptide that is co-localized with NE.<sup>61</sup> In postmortem studies of suicide victims who had a likely diagnosis of depression, concentrations of neuropeptide Y immunoreactivity were significantly reduced in the frontal cortex and caudate nucleus.<sup>62</sup> Treatment with NRIs such as desipramine results in decreased neuropeptide Y receptor density that could possibly be due to an increase in neuropeptide Y levels.<sup>63</sup> Somatostatin, a tetradecapeptide, is found in high concentrations in the hypothalamus, amygdala, and nucleus accumbens. It is involved in NE and dopamine neurotransmission.<sup>64</sup> Depressed patients show decreased cerebral spinal fluid concentrations of somatostatin,<sup>65,66</sup> a nonspecific finding since it is also decreased in a variety of other neuropsychiatric illnesses.<sup>64</sup> Chronic desipramine dosing in rats resulted in increased somatostatin receptors in the nucleus accumbens.<sup>67</sup>

Excitatory amino acids such as glutamate and aspartate act through the NMDA and non-NMDA receptors. They influence monoamine transmission including dopamine and NE and are in turn influenced by these catecholamines.<sup>68</sup> Recently, the glutamate system has been shown to have a direct stimulatory effect on noradrenergic neurons,<sup>69</sup> and the interaction between excitatory amino acids and NE is another promising area for further study into the underlying cause of depression. Chronic, but not acute, administration of noncompetitive NMDA antagonists is associated with decreased density of  $\beta$ -adrenergic receptors in the mouse cortex.<sup>70</sup> Chronic desipramine binding has been shown to increase total NMDA receptor binding.<sup>71</sup>

The role of NE in depression should be interpreted in the context of its interaction with other modulatory factors that may also be involved in depression. One implication of such an assessment is that a unitary cause of the pathophysiology of all cases of depression or antidepressant drug action is unlikely to be found. Rather, it should be recognized that an inherent heterogeneity exists in the etiology of depression and mechanism of antidepressant drug action.

#### **EFFECT OF NOREPINEPHRINE ON INTRACELLULAR SIGNAL TRANSDUCTION PATHWAYS**

Wachtel<sup>72</sup> postulated that a dysregulation of neuronal second messenger function is involved in depression. This hypothesis suggests that, in depression, an abnormality in the major second messenger systems in the CNS results from diminished adenylate cyclase pathway and increased phospholipase C pathway activities. The roles of signal transduction pathways and ultimately genomic factors have been emphasized in recent theories of the mechanism of action of antidepressants.<sup>4,48,73</sup> It has been hypothesized that although  $\beta$ -adrenergic receptors are down-regulated after antidepressant treatment, there is a net effect of increased cAMP (cyclic adenosine 3',5'-monophosphate) production by antidepressants, leading to increased signal transduction.<sup>73</sup> Agents that increase cAMP directly, e.g., phosphodiesterase inhibitors such as rolipram and papaverine, have been found to have some antidepressant activity. Beside the cAMP pathway, other second messenger pathways such as the phosphatidylinositol pathway have been implicated. Inositol, a precursor of the second messenger system of inositol phosphate, has been reported to be useful for the treatment of depression.<sup>74</sup> More work needs to be done to replicate these findings.

The antidepressant activity of increased cAMP levels may also be mediated through an increase in cAMP response element-binding protein that increases neurotrophic factor production.<sup>73</sup>

#### **EFFECT OF NOREPINEPHRINE ON NEUROTROPHIC FACTORS**

Recently, a number of different proteins called nerve growth factors have been discovered. These proteins have been shown to affect the differentiation and growth of neurons in the developing brain as well as the maintenance and survival of neurons in the mature brain. In preclinical studies, brain-derived neurotrophic factor and its receptor trkB have been shown to increase with ECT. Brain-derived neurotrophic factor mRNA is also increased with chronic administration of several different classes of antidepressant drugs, but not with the acute administration of these drugs or by administration of psychotropic drugs without antidepressant effects.<sup>75</sup> Local infusion of brain-derived neurotrophic factor in the brain has been shown to have antidepressant effects in 2 behavioral models of depression—the forced-swim and learned-helplessness paradigms.<sup>76</sup> Therefore, the mechanism of action of antidepressants may involve increase in production of neurotrophins such as brain-derived neurotrophic factor and neurotrophin-3. Their putative antidepressant effects may be a result of the ability of neurotrophins to increase monoaminergic neurotransmission and to increase the survival of monoamine neurons. Brain-derived neurotrophic factor has been shown to increase 5-HT neurotransmission<sup>77</sup> and to protect serotonin neurons from neurotoxin-induced damage,<sup>78</sup> and neurotrophin-3 has been noted to have similar effects on noradrenergic neurons.<sup>79,80</sup> In this regard, Klimek and colleagues<sup>81</sup> recently reported a decreased number of norepinephrine transporter sites in the locus ceruleus in postmortem specimens of depressed individuals. Since the number of transporter sites are an indirect indicator of the viability of NE neurons, the Klimek study suggests there may be a decreased number of noradrenergic neurons in the locus ceruleus of depressed individuals.

In addition, a number of recent studies have brought attention to evidence of nerve cell and glial loss in different brain regions in depression, e.g., the hippocampus, locus ceruleus, and the anterior cingulate prefrontal cortex.<sup>81-84</sup> This effect could be due to stress-related nerve cell damage or to effects of depression, e.g., increased cortisol levels. Neurotrophic factors released by the chronic action of antidepressants could decrease this effect and prevent the precipitation and perpetuation of depression. Medications that directly increase neurotrophic factors in particular areas of the brain, e.g., the hippocampus, and drugs that act on their receptors, e.g., the trkB receptors, would be expected to have antidepressant activity and may have a much more rapid antidepressant effect compared with traditional antidepressants.<sup>73</sup>

In summary, antidepressants that increase NE levels may also prevent neuronal atrophy in cortical brain areas by increasing the levels of nerve growth factors. Nerve growth factors themselves may augment the effects of NRIs.

Table 1. Therapeutic Strategies Related to Norepinephrine Dysfunction in Depression<sup>a</sup>

Norepinephrine Function	Abnormality Seen in Depression	Therapeutic Strategies
NE production and release	Possible decreased production	Monoamine reuptake inhibitors and selective NRIs
$\alpha$ Receptor	Increased presynaptic $\alpha_2$ -receptor sensitivity (neuroendocrine response to yohimbine)	$\alpha_2$ Antagonists such as yohimbine may augment effects of other antidepressants
	Decreased postsynaptic $\alpha_2$ -receptor sensitivity (GH response to clonidine)	Lithium, but not antidepressants, reverses this effect
$\beta$ Receptor	Possible $\beta$ -receptor up-regulation in depression	$\beta$ receptors down-regulated by most antidepressants
		Combination of NRIs with SSRIs for a more rapid down-regulation of $\beta$ receptors
Interaction with other neurotransmitters and neuropeptides	Adrenergic heteroreceptors on 5-HT neurons can decrease 5-HT release	Antagonists of NE heteroreceptors, eg, mianserin, mirtazapine
	NE and glutamate interactions	Glutamate antagonists may have antidepressant effects
	Chronic activation of LC by CRH may lead to NE depletion in LC	CRH antagonists; desipramine reverses effects of CRH
Signal transduction pathways	Common effect of many antidepressants is to increase second messenger (eg, cAMP, PIP) signal transduction	Phosphodiesterases such as papaverine and rolipram may augment effect of NRIs; inositol may be used as an augmenting agent
Nerve growth factors	Many antidepressants increase levels of NGFs	NGFs such as BDNF and NT-3 or their derivatives may be used as augmenting agents for rapid treatment of depression
	Chronic stress associated with decrease in nerve growth factors and cell death	NRIs that increase NE and NGFs may decrease neuronal loss associated with depression

<sup>a</sup>Abbreviations: 5-HT = serotonin, BDNF = brain-derived neurotrophic factor, cAMP = cyclic adenosine monophosphate, CRH = corticotropin-releasing hormone, GH = growth hormone, LC = locus ceruleus, NE = norepinephrine, NGF = nerve growth factor, NRI = norepinephrine reuptake inhibitor, NT-3 = neurotrophin-3, PIP = phosphatidylinositol, SSRI = selective serotonin reuptake inhibitor.

### NEW NOREPINEPHRINE THERAPEUTIC STRATEGIES IN DEPRESSION

Findings from the studies reviewed above suggest a critical role of NE in the pathophysiology of depression. Evidence suggests that NE deficiency is associated with depression, that adrenergic receptor function may be altered in depression, and that antidepressants frequently lead to changes in these receptors. Chronic stress may be an important precipitating factor in depression, and stress-related chronic stimulation of the locus ceruleus may lead to NE depletion. This effect is reversed by antidepressants. Therefore, drugs that increase NE such as the NRIs may be particularly effective since they act directly on the locus ceruleus. Furthermore, abnormalities in signal transduction mechanisms by which NE effects on postsynaptic receptors are translated into intracellular events may be present in depression. Finally, stress decreases neurotrophic factors that maintain neuronal viability. Antidepressants that increase NE have been shown to increase neurotrophic factors and may prevent neuronal loss in the locus ceruleus as well as other brain regions that regulate mood.

New therapeutic strategies are suggested by the findings of the studies reviewed above (Table 1). Some of these strategies have already been studied and some need further investigation.

NE reuptake inhibition with NRIs seems to be the most successful way to increase synaptic NE levels and achieve antidepressant action. Reboxetine, the most selective of the NRIs, has been found to be clinically effective in the treatment of depression.<sup>85-89</sup>

Both NRIs and SSRIs down-regulate  $\beta$ -adrenergic receptors. Therefore, it was thought that a combination of the two may have a more rapid onset of action<sup>90</sup> or be more effective in the treatment of depression resistant to either class of antidepressants. Fava and colleagues,<sup>91</sup> however, reported that an increased dosage of fluoxetine was better than a combination of fluoxetine and desipramine or a combination of desipramine and lithium in the treatment of refractory depression. A preliminary study in which patients were given 3 trials of fluoxetine or desipramine or a combination of both failed to support the increased efficacy of the combination.<sup>92</sup> Recently, a number of drugs that are both selective serotonin and norepinephrine uptake inhibitors have been developed. Venlafaxine, a new antidepressant that is an SSRI and an NRI is one of the most potent inhibitors of  $\beta$ -adrenergic receptors. Because of this property, it was thought that venlafaxine may lead to a more rapid antidepressant response or be a more effective antidepressant. Preliminary studies<sup>93</sup> do suggest that venlafaxine may be useful in the treatment of depression refractory to conventional antidepressants at dosages at which it acts as both an NRI as well as an SSRI.

Preclinical and clinical studies of antidepressant action have uncovered some methods that may increase the efficacy or rapidity of action of antidepressants. For example, it was thought that the antidepressant action of TCAs such as desipramine could be augmented with yohimbine, which would inhibit presynaptic  $\alpha_2$ -adrenergic receptors and thereby increase the amount of synaptic NE. However, augmentation of desipramine with yohimbine to treat refractory depression failed to support this hypothesis.<sup>51</sup> Sachs and colleagues<sup>94</sup> reported improvement in 3 patients pre-

treated with yohimbine before ECT; however, manic symptoms have been reported in bipolar patients given yohimbine.<sup>95</sup> Recent controlled studies with idazoxan, a selective  $\alpha_2$ -antagonist, indicate it may have antidepressant effects.<sup>96</sup> Finally, Harkin and colleagues<sup>97</sup> found, in a number of animal models of depression, that a combination of reboxetine and sertraline yielded a more rapid onset of response than either reboxetine or sertraline treatment alone.

Presynaptic  $\alpha_2$ -adrenergic receptors (heteroreceptors) are also present on serotonergic neurons and exert a tonic inhibitory influence on 5-HT transmission.<sup>6</sup> Drugs such as mianserin and mirtazapine, which possess presynaptic  $\alpha_2$ -adrenergic receptor antagonist activity, have been shown to have antidepressant properties.<sup>98</sup> These properties may be due to the ability of these drugs to increase both adrenergic and serotonergic transmission.

Phosphodiesterase inhibitors such as rolipram and piperazine that increase cAMP levels have been noted to have antidepressant properties.<sup>99,100</sup> Development of new pharmacologic agents that target cAMP response element-binding protein and the nerve growth factors brain-derived neurotrophic factor and neurotrophin-3 or their receptors, e.g., the trkB receptor, may find a role in depression therapy either as stand-alone or augmenting agents.<sup>73</sup>

The effect of stress on neuronal viability and its possible role in the precipitation and perpetuation of depression suggests that factors that decrease the effects of stress such as CRH antagonists, nerve growth factors, or antiglutamatergic agents may be helpful in preventing depression and its sequelae. Recent preclinical experiments of NE neuron transplantation in the brain further support the role of NE in depression. Implantation of bovine chromaffin cells in rat frontal cortex resulted in antidepressant effects in animal models of depression. The antidepressant effects were related to elevated levels of NE and epinephrine but not dopamine.<sup>101</sup>

## CONCLUSION

In conclusion, the study of the noradrenergic system remains one of the cornerstones of depression research. Better understanding of the action of catecholamines at the synaptic and intracellular level holds the potential for providing clues to the etiology of depression and development of more efficacious psychopharmacologic treatments of depression. Medications that increase NE availability are potentially one of the most effective classes of antidepressants available for the treatment of depression and merit more extensive study in clinical settings.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), clonidine (Catapres and others), desipramine (Norpramin and others), fluoxetine (Prozac), maprotiline (Ludomil), mirtazapine (Remeron), phenelzine (Nardil), propranolol (Inderal and others), reboxetine (Vestra), reserpine (Serpasil and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others).

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