

# The importance of norepinephrine in depression

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**Abstract:** Depression is one of the most common psychological diseases with significant potential morbidity and mortality. Although the underlying pathophysiology of depression has not been clearly defined, preclinical and clinical evidence suggest disturbances in serotonin (5-HT), norepinephrine (NE), and dopamine (DA) neurotransmission in the central nervous system. Virtually all currently available antidepressants act on one or more of the following mechanisms: inhibition of reuptake of 5-HT or NE (and DA), antagonism of inhibitory pre-synaptic 5-HT or NE receptors, or inhibition of monoamine oxidase. All of these mechanisms result in an enhanced neurotransmission of 5-HT and/or NE. Evidence for the involvement of NE in depression is abundant, and recent studies on neuronal pathways and symptoms highlight the specific role of NE in this disorder. NE plays a determinant role in executive functioning regulating cognition, motivation, and intellect, which are fundamental in social relationships. Social dysfunction is possibly one of the most important factors affecting the quality of life in depressed patients.

**Keywords:** serotonin, antidepressants, neurotransmission, symptoms

## Introduction

Depression is associated with significant potential morbidity and mortality contributing to suicide, medical illness, disruption of interpersonal relationships, lost work time, and often leading to substance abuse.<sup>1</sup> The underlying pathophysiology of depression is not clearly understood, but biological, psychological, and social factors all play a causal role in depression.<sup>2</sup>

Imaging studies have shown that patients with depression have smaller hippocampal volume compared with controls,<sup>3</sup> and there may be a link between depression and hippocampal neurogenesis.<sup>4</sup> Evidence also suggests that major depression may involve an overactive hypothalamic-pituitary-adrenal axis which results in an effect similar to the neuroendocrine response to stress.<sup>5</sup> The hormone, estrogen, has also been implicated in depressive disorders<sup>6-8</sup> and in their treatment.<sup>9</sup> The involvement of pro-inflammatory cytokines in depression is strongly suggested by meta-analyses of clinical studies showing higher blood concentrations of interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  in depressed patients compared with controls.<sup>10,11</sup> Other possible disease mechanisms that have been suggested include changes in glutamatergic neurotransmission, reduced neurotransmission of gamma-butyric acid, abnormal circadian rhythms, deficient neurosteroid synthesis, impaired endogenous opioid function, acetylcholine imbalance, tyroxine abnormalities, and dysfunction of specific brain structures and circuits.<sup>12</sup> In spite of these new hypotheses, one of

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the oldest, the monoamine hypothesis which postulates a deficiency of serotonin (5-HT) and/or norepinephrine (NE) neurotransmission in the brain,<sup>13,14</sup> is still driving clinical development of new antidepressants. Virtually all currently available antidepressants act on one or more mechanisms compatible with the monoamine hypothesis: inhibition of reuptake of 5-HT or NE; antagonism of presynaptic inhibitory 5-HT or NE receptors; or inhibition of monoamine oxidase. All of these mechanisms result in an enhanced neurotransmission of 5-HT and/or NE. The confirmation of the clinical activity of these antidepressants has done much to reinforce the monoamine hypothesis.

An association of specific features and symptoms of depression and a deficiency or dysfunction of certain neurotransmitters has been proposed.<sup>15</sup> Thus, a 5-HT deficiency is related to anxiety, obsessions, and compulsions; reduced NE neurotransmission is associated with decreased alertness, low energy, problems of inattention, concentration, and cognitive ability; while dysfunctional dopamine (DA) activity is implicated in problems of motivation, pleasure, and reward. Interestingly, increased 5-HT activity can be associated with certain symptoms such as fatigue.<sup>16</sup>

Evidence for the involvement of 5-HT in depression has been the subject of numerous studies.<sup>17</sup> The role of NE<sup>15,18</sup> and DA<sup>19,20</sup> has been less extensively studied. This review briefly summarizes the involvement of NE in depression, highlighting the importance of the relationship between NE pathways and specific symptoms.

## Evidence for the involvement of NE in depression

Several lines of evidence suggest that NE is a neurotransmitter of major importance in the pathophysiology and treatment of depressive disorders.<sup>21</sup>

1. NE projections from the locus coeruleus innervate the limbic system, which is implicated in the regulation of emotions.
2. Numerous differences have been found in elements of the NE system in postmortem brains from depressed patients and healthy controls.
3. Genetic studies show that mice with genetically engineered functional enhancement of the NE system are protected from stress-induced depression-like behaviors.
4. Experimental depletion of NE in the brain results in a return of depressive symptoms after successful treatment with NE antidepressant drugs.
5. Therapeutic agents which specifically increase NE activity are effective antidepressants.

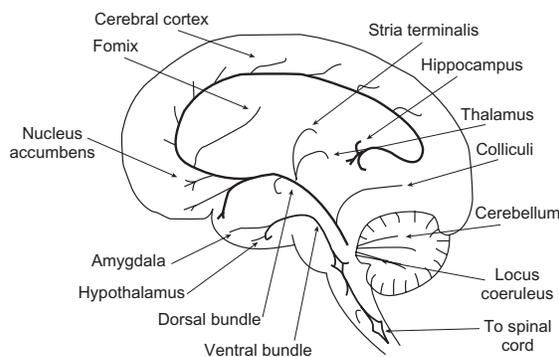
## NE neuroanatomy

Noradrenergic pathways in the brain arise from the cell bodies in the locus coeruleus and project to different cerebral regions and to the spinal cord (Figure 1). In addition to major projections to the frontal cortex, NE neurons project to the limbic system, whose various components such as the amygdala, hippocampus, and hypothalamus are implicated in emotion and cognition as well as a number of functions modified in depressed patients such as appetite, response to pain, levels of pleasure, sexual satisfaction, and aggressive behavior.<sup>22</sup>

Imaging studies indicate that major depression is associated with abnormal metabolism in limbic and paralimbic structures of the prefrontal cortex. This abnormal metabolism is normalized in the amygdala and prefrontal cortex in patients showing a persistent antidepressant response.<sup>22</sup>

Stahl<sup>23</sup> has suggested that it can be instructive to consider brain neuroanatomy in terms of specific functional centers (Table 1).<sup>23–26</sup> The “emotional” and “somatic” centers in the brain receive projections from both NE and 5-HT as well as DA pathways. The “cognitive” centers, on the other hand, receive input only from NE as well as DA and histaminergic projections, but not 5-HT projections.<sup>23–26</sup>

Executive function is a complex organization of higher mental functions that process mental and environmental input to enable efficient problem-solving capacity in a way that is acceptable to both the individual and society. It includes inhibition of irrelevant or unacceptable behavior, the suppression of nonpertinent information, the regulation of verbal and nonverbal working memory, self-regulation of affect, motivation and arousal, planning, decision-making, self-monitoring of the problem-solving process, and self-evaluation of the results of the action taken. Anatomically, this occurs in the prefrontal lobe of the cortex and its afferent and efferent



**Figure 1** Sagittal section of the human brain, showing the principal noradrenergic pathways. Adapted with permission from Moret C. Understanding neurotransmission in the brain. Available from: [http://www.psy-world.com/unt\\_noradr.htm](http://www.psy-world.com/unt_noradr.htm).

**Table 1** Neuronal projections to different brain “centers”**Emotional centers**

NE projections from the locus coeruleus to the hypothalamus  
 NE projections from the locus coeruleus to the amygdala and prefrontal cortex  
 5-HT projections from the midbrain raphe to the hypothalamus  
 5-HT projections from the midbrain raphe to the amygdala and prefrontal cortex  
 DA projections from the ventral tegmentum to the nucleus accumbens

**Somatic centers**

NE projections from the locus coeruleus to the hypothalamus  
 NE projections from the locus coeruleus to the cerebellum  
 NE projections from the locus coeruleus to the spinal cord  
 5-HT projections from the midbrain raphe to the hypothalamus  
 5-HT projections from the midbrain raphe to the striatum  
 5-HT projections from the midbrain raphe to the spinal cord  
 DA projections from the substantia nigra to the striatum

**Cognitive centers**

NE projections from the locus coeruleus to the dorsolateral prefrontal cortex  
 DA projections from the ventral tegmentum to the dorsolateral prefrontal cortex  
 Histamine projections from the hypothalamus to the dorsolateral prefrontal cortex

**Source:** Summarized from references 23–26.

**Abbreviations:** 5-HT, serotonin; DA, dopamine; NE, norepinephrine.

structures involving the neurotransmitters NE and DA and to a lesser degree acetylcholine and 5-HT.<sup>27</sup>

Executive function is also fundamental to social relationships. Social dysfunction in depression is possibly one of the most important factors affecting the quality of life of patients. Considerable clinical data suggest the importance of NE in the improvement of clinical dysfunction in depression.<sup>28</sup>

## Biochemical differences between depressed patients and healthy controls

An early study<sup>29</sup> found increased  $\beta$ -adrenergic receptor binding in the frontal cortex of suicide victims. More recently, post-mortem and functional imaging studies in the prefrontal cortex of depressed suicide victims have shown altered density and sensitivity of  $\alpha_{2A}$ -adrenoceptors which modulate NE release.<sup>30–32</sup> In addition, decreased NE transporter binding has been reported in locus coeruleus of postmortem samples from subjects diagnosed with major depression.<sup>33</sup> Alterations in putative peripheral markers of central NE function, such as  $\alpha_2$ -adrenoceptor density in platelets, have also been found in depressed patients.<sup>34,35</sup> These modifications may all be part of the primary causal physiopathology of depression. Alternatively, at least some of them could be the result of compensatory modifications resulting from changes of NE neurotransmission in depressed patients. Whatever the interpretation, these data imply an important role for NE in depression.

## Genetic studies of NE function

Genetic studies of NE function have indicated the multiple roles that NE plays in normal and pathological states. Functional deletion (knockout) of the NE transporter in mice results in increased extracellular levels of NE.<sup>36</sup> This model functionally mimics the therapeutic effects of selective NE antidepressants. Recently, this model has shown that NE transporter (NET) knockout mice are resistant to the stress-induced depressive-like changes in behavior and brain neurotrophin expression that are seen in wild-type mice.<sup>37</sup> Human genetic studies have shown that variations in the gene coding for NET which alter neurotransmitter release are related to individual differences in behavior and susceptibility to depression.<sup>38</sup> The polymorphism, NET-T182C, for example, is associated with an increased susceptibility to depression.<sup>39</sup>

Catechol-O-methyltransferase (COMT) 158Val/Met is a polymorphism of a major enzyme in catecholamine inactivation. The alleles encoding Val and Met are associated with relatively high and relatively low COMT activity, respectively. The Val/Val genotype, a high-activity COMT genotype, was significantly less frequent in male suicide completers than in male controls.<sup>40</sup> An association of 158Val/Met polymorphism with major depression is still unclear, since some studies have found the Met allele (low COMT activity) to be associated with major depression<sup>41</sup> while others have not.<sup>42,43</sup>

## NE depletion studies

Studies in depressed patients in remission and no longer taking medication have shown that a drastic reduction of NE levels (by inhibition of the key synthetic enzyme, tyrosine hydroxylase, with  $\alpha$ -methyl-p-tyrosine) results in a rapid reappearance of depressive symptoms. Interestingly, however, catecholamine depletion in healthy control volunteers does not result in depressed mood.<sup>18,44,45</sup>

## Clinical activity of noradrenergic antidepressants

A considerable proportion of patients fail to respond adequately to selective serotonin reuptake inhibitors (SSRIs). Analysis of the unresolved symptoms suggests that a specific set of symptoms related to decreased positive affect respond poorly to serotonergic antidepressants, namely loss of pleasure, loss of interest, fatigue, and loss of energy.<sup>46</sup> There is evidence to suggest that antidepressants that enhance NE and DA activity offer a therapeutic advantage over 5-HT antidepressants in the treatment of symptoms associated with reduced positive affect.

The undisputed antidepressant action of NE-selective tricyclic antidepressants such as desipramine and nortriptyline suggests a major involvement of NE neurotransmission in depression, although these compounds or their metabolites also have some action on the 5-HT system. The selective NE reuptake inhibitor, reboxetine, has demonstrated equivalent efficacy to the TCA (tricyclic antidepressants) in some studies<sup>47,48</sup> and is approved as an antidepressant in Europe but not in the USA. A recent publication<sup>49</sup> suggests, however, that there may be considerable publication bias and that if unpublished studies are also considered, the antidepressant activity is unclear.

The SNRIs (serotonin and norepinephrine reuptake inhibitors) venlafaxine, milnacipran, and duloxetine show at least equivalent antidepressant efficacy to the SSRIs, and there is evidence that they may be more effective than the SSRIs in achieving remission.<sup>50</sup>

## Conclusion

Although 5-HT has been the most studied neurotransmitter in depression, converging lines of evidence suggest that NE is of major importance in the pathophysiology and treatment of depressive disorder. NE projections from the locus coeruleus innervate the limbic system, which is implicated in the regulation of emotions and cognition. Substantial functional biochemical differences exist in the NE system in postmortem brains from depressed patients and healthy controls. Genetic manipulation of the NE system that increases NE neurotransmission protects animals from stress-induced depressive behavior, while chemical manipulation that depletes the brain of NE increases the susceptibility of recovered depressed patients to a depressive relapse. Therapeutic agents which specifically increase NE activity are effective antidepressants, and there is evidence that those acting simultaneously on 5-HT and NE neurotransmission may have an antidepressant action superior to SSRIs.<sup>50</sup>

## Disclosure

Dr Chantal Moret has no potential conflict of interest. Dr Mike Briley is a consultant for Pierre Fabre Médicament, Asahi Kasei Pharma, Germania Pharmaceutica, Janssen Pharmaceutica, and Cypress BioScience.

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