The importance of norepinephrine in depression

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 presynaptic 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. The underlying pathophysiology of depression is not clearly understood, but biological, psychological, and social factors all play a causal role in depression.

Imaging studies have shown that patients with depression have smaller hippocampal volume compared with controls, and there may be a link between depression and hippocampal neurogenesis. 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. The hormone, estrogen, has also been implicated in depressive disorders and in their treatment. 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)-α in depressed patients compared with controls. 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. In spite of these new hypotheses, one of
the oldest, the monoamine hypothesis which postulates a
deficiency of serotonin (5-HT) and/or norepinephrine (NE)
neurotransmission in the brain,13,14 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 monoam-
one 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 neu-
rotransmitters has been proposed.15 Thus, a 5-HT deficiency
leads to feelings of sadness, irritability, and loss of
interest; while a deficiency of NE results in low energy, con-
fusion, and feelings of sadness. The confirmation of the
clinical activity of these antidepressants has done much
to reinforce the monoamine hypothesis.

Evidence for the involvement of 5-HT in depression has
been the subject of numerous studies.17 The role of NE15,18
and DA19,20 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 neurotransmit-
ter of major importance in the pathophysiology and treatment
of depressive disorders.21
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 engi-
eered functional enhancement of the NE system are pro-
tected 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 cere-
bral 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.22

Imaging studies indicate that major depression is asso-
ciated with abnormal metabolism in limbic and paralimbic
structures of the prefrontal cortex. This abnormal metabo-
lism is normalized in the amygdala and prefrontal cortex in
patients showing a persistent antidepressant response.22

Stahl23 has suggested that it can be instructive to consider
brain neuroanatomy in terms of specific functional centers
(Table 1).23–26 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.21–26

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 suppres-
sion of nonpertinent information, the regulation of verbal and
nonverbal working memory, self-regulation of affect, motiva-
tion 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.
structures involving the neurotransmitters NE and DA and to a lesser degree acetylcholine and 5-HT.27

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.28

### Biochemical differences between depressed patients and healthy controls

An early study29 found increased β-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 α2-adrenoceptors which modulate NE release.30–32 In addition, decreased NE transporter binding has been reported in locus coeruleus of postmortem samples from subjects diagnosed with major depression.33 Alterations in putative peripheral markers of central NE function, such as α2-adrenoceptor density in platelets, have also been found in depressed patients.34,35 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.36 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.37 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.38 The polymorphism, NET-T182C, for example, is associated with an increased susceptibility to depression.39

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.40 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 depression41 while others have not.42,43

### 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 α-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.18,44,45

### 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.46 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\(^7,8\) and is approved as an antidepressant in Europe but not in the USA. A recent publication\(^9\) 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.\(^{50}\)

**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.\(^{50}\)

**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.

**References**