Evidence for a Biochemical Lesion in Depression

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The monoamine hypothesis of depression predicts an impairment in central monoaminergic function. The lesion may comprise deficiencies in the absolute concentrations of norepinephrine and/or serotonin (5-HT). Depletion studies have shown a correlation between such deficiencies and depressive symptoms. Measurement of the concentrations of the neurotransmitters and their metabolites in cerebrospinal fluid, urine, and plasma of patients with depression has yielded equivocal results regarding the possibility of altered metabolism of these neurotransmitters. Other studies have investigated the possibility of altered numbers and/or affinities of the serotonin and norepinephrine receptors and uptake sites. For example, there is evidence for a reduction in the activity of the serotonin reuptake transporter in patients with depression and an increase in the density of 5-HT_2 receptors in the brains of suicide victims. Similarly, in the noradrenergic system, up-regulation of β-adrenoceptors is consistently observed. Most recently, attention has focused on the possibility that a lesion may occur in the postreceptor, subcellular components of the monoamine systems, such as the second messenger processes. Also, experimental evidence has shown "cross-talk" between the noradrenergic and serotonergic systems. There is therefore substantial clinical and experimental evidence that lesions in the serotonergic and noradrenergic systems are responsible for depression and that antidepressant treatment can reverse these alterations.
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The basis of the monoamine hypothesis of depression is the assumption that there is an impairment in central monoaminergic function. This impairment may be due to a "lesion" in one or more of a variety of biochemical processes. For example, monoamine concentrations may be altered as a result of disrupted synthesis, storage, or release. Alternatively, the concentrations may be normal but the postsynaptic receptors and/or the subcellular messenger activity may be impaired. The 3 major monoamine neurotransmitters—serotonin (5-HT), norepinephrine, and dopamine—affect a range of symptoms, such as vigilance, motivation, euphoria, appetite, and impulse, to varying degrees, thereby influencing not only depressive states but also other major psychiatric illnesses.

The main approaches to investigating any correlation between monoamine system dysfunction and depressive symptoms have involved measurement of the monoamines or their metabolites in body fluids, measurements of monoamines or their receptors in postmortem brain tissue, indirect measurements of receptor function by assessing hormone changes, and study of changes that occur following the depletion of brain monoamines. This article reviews the current evidence that a biochemical lesion in the norepinephrine or serotonin neuronal systems is involved in depression (Figure 1).

METABOLISM

Indications of dysfunctional metabolism of monoamine neurotransmitters come from measurement of the metabolites in body fluids. The concentrations of the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), have been investigated in the urine, plasma, and cerebrospinal fluid (CSF) of patients with depression, but no clear conclusions have been reached. While some studies have found an increased urinary concentration of MHPG in patients with depression,[1] others have found a decrease[2,3] or no change.[4,5] Measurement of the plasma MHPG concentration has also proved an unreliable method of assessing noradrenergic activity. In addition, studies of CSF concentrations have yielded equivocal results with respect to MHPG.[6] Norepinephrine concentrations in CSF in patients with depression have been shown to be no different from those in control subjects.[7–9]

Similarly, regarding the serotonergic system, concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in CSF are reported to be lowered in patients with depression, although this is not consistently ob-

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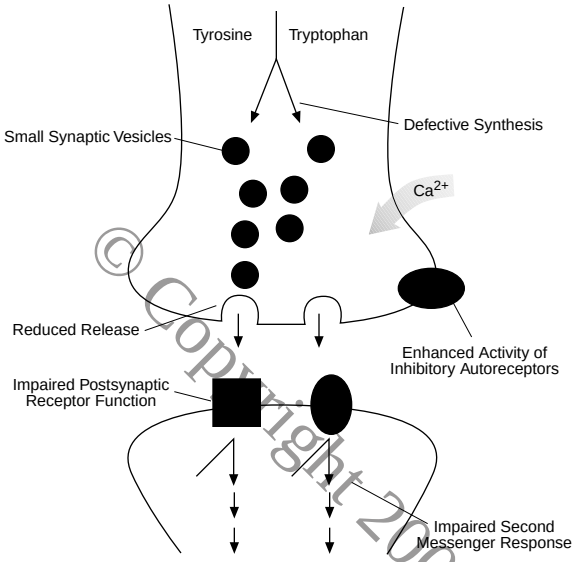
Figure 1. Possible Sites of Biochemical Lesion in Neurons in Patients With Depression



served. Low concentrations in the CSF and cortex have been found to correlate with violent suicide.[10,11] Several studies have investigated the possibility that concentrations of serotonin metabolites correlate with severity of depression. Most have found no link. However, a negative correlation has been demonstrated between severity and 5-HIAA concentrations in the CSF.[12,13] The concentration of serotonin itself has been shown to be significantly reduced in the hypothalamus and amygdala of postmortem brain tissue of patients who had depression.[14]

The possible consequences of defective synthesis of norepinephrine and serotonin have been demonstrated by monoamine depletion studies. For example, norepinephrine synthesis may be interrupted by addition of α-methylparatyrosine (AMPT) to the diet, thereby blocking the conversion of tyrosine to L-3,4-dihydroxyphenylalanine (L-dopa) and hence causing a depletion of norepinephrine.[15] Similarly, rapid depletion of dietary tryptophan leads to a lowering of serotonin.[16] These studies have shown that the effect of depletion depends on the antidepressant treatment received by the patient. Patients treated with a selective serotonin reuptake inhibitor (SSRI) were vulnerable to tryptophan depletion only, while those treated with a primarily noradrenergic reuptake inhibitor (such as desipramine) were susceptible to AMPT treatment only. Healthy controls or unmedicated depressed patients were unaffected by the monoamine depletions.[17] These results suggest that altered concentrations of individual monoamines are not necessarily the primary cause of depression and that there may be adaptive changes in the monoamine systems in the brain. It has also been proposed that antidepressant drugs, whether primarily noradrenergic or serotonergic in their specificities, may act through a common neuronal system.[15]

ENZYME ACTION

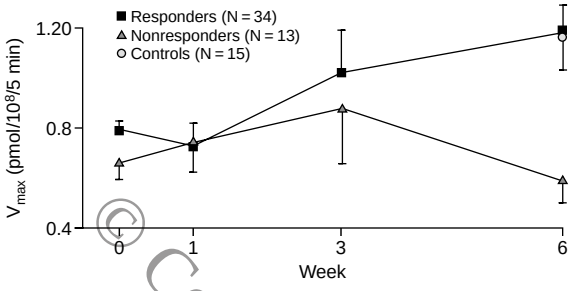
Impaired enzyme activity may play a role in depression, although reports are few. Tyrosine hydroxylase, an enzyme essential for norepinephrine synthesis, has been reported to be up-regulated in animal models of depression and down-regulated by imipramine treatment.[18,19] Contradictory findings have been reported from studies of the concentration of tyrosine hydroxylase in the locus ceruleus of suicide victims: both decreases[20] and increases[21] have been reported. Chronic tricyclic antidepressant (TCA) administration has been found to decrease tyrosine hydroxylase concentrations in the locus ceruleus of the rat.[18,22] It has therefore been suggested that there is normal norepinephrine synthesis in depression and that antidepressants may act at the level of tyrosine hydroxylase gene expression.[23] Studies of the monoamine oxidase enzymes have so far found no abnormalities in their activities.[24]

REUPTAKE TRANSPORTERS

The monoamine reuptake transporters are the target of some of the newest forms of antidepressant pharmacotherapy—the SSRIs and the new selective norepinephrine reuptake inhibitor, reboxetine. Much of the evidence for the dysfunction of the serotonin reuptake transporters in depression is indirect, since studies of the transporter have mostly been conducted using platelets from patients with depression. The serotonin transporter complex present in the brain has been shown to be identical to that in platelets.[25] Studies have shown that the binding of radiolabeled imipramine is significantly reduced in patients with depression, mainly due to decreased numbers of binding sites on the platelet membranes.[26,27] Indeed, probably the most consistent observation is that activity of the serotonin transporter in platelets is reduced in patients with depression.[28] Furthermore, the reduction may be specific to major depression, since no changes in [^{3}H]-imipramine binding to platelets were found in patients with panic disorder, mania, Alzheimer's disease, or atypical depression.[28]

Several studies have assessed serotonin uptake sites using radiolabeled imipramine binding in the postmortem brain tissue of suicide victims and patients with depression, but the results have been equivocal, possibly due to inconsistencies in the selection of subjects or to nonspecific imipramine binding.[29] Changes in the transporter have been found to correlate with response to treatment. As patients respond to antidepressant treatment, the number of imipramine binding sites on platelets has been shown to increase.[28,30] Reduced platelet serotonin uptake rates were found to return to normal in patients with de-

Figure 2. [^{3}H]-Serotonin Uptake in Platelets From Patients With Depression After Treatment With Trazodone or Amitriptyline[a]



[a]Data from Healy et al.[32]

pression who responded to amitriptyline or trazodone, but remained low in nonresponding patients (Figure 2).[31,32]

More recently, in a study using single photon emission computed tomography, the radiolabeled tracer [^{123}I]β-CIT has been used to investigate the serotonin transporter in the brains of patients with depression.[33] The tracer binds with high affinity to the serotonin transporter in the midbrain. In this study, a reduction in the activity of the transporter was seen in patients with depression, compared with healthy controls. There is evidence that expression of the transporter is modified by antidepressant treatment: imipramine, fluoxetine, clomipramine, and desipramine have been shown to reduce expression.[34]

A possible genetic basis for dysfunctional serotonin transporters has also been discovered. Transcription of the human transporter gene has been found to be impaired by an abnormality in the promoter region. In particular, a short allele variant has been found to reduce the transcriptional efficiency of the gene, and there appears to be an increased occurrence of this allele in patients with unipolar depression.[35,36]

With respect to the noradrenergic system, few studies have been conducted to measure the norepinephrine reuptake sites. In one study,[37] no difference was found between suicide victims and controls in the extent of radiolabeled desipramine binding in brain tissue. Another study[38] found significantly reduced binding of radiolabeled [^{3}H]nisoxetine in the postmortem locus ceruleus tissue from suicide victims and patients with depression, compared with control subjects. In a study of bipolar depression,[39] no evidence was found for any correlation with changes in norepinephrine transporter gene expression.

PRESYNAPTIC AND POSTSYNAPTIC RECEPTORS

Serotonin Receptors

The most extensively studied receptors, with regard to the lesion involving a dysfunction in the serotonergic system, have been 5-HT$_1$ and 5-HT$_2$ types. A reduction in the number of 5-HT$_1$ receptors has been reported in the hippocampus of antidepressant-free suicide victims compared with controls, while an increase in the number of binding sites, but decrease in the binding affinity, was observed in antidepressant-treated compared with untreated suicide victims.[40] The binding of 5-HT$_{1A}$ receptors has been reported to be increased in the midbrain dorsal raphe nucleus of suicide victims known to have had depression.[41] Other studies have found no difference in the number of receptors in the frontal cortex, occipital cortex, hippocampus, or amygdala tissue in suicide victims compared with controls.[40–43]

No consistent correlations between 5-HT$_2$ receptor binding and depressive illness have been observed. A higher density of 5-HT$_2$ receptors has been reported in the frontal cortex of suicide victims compared with controls,[44,45] although other studies have found no difference.[46,47] Binding of 5-HT$_2$ receptors using the radioligand [^{18}F]altanserin and positron emission tomography has been shown to be significantly reduced in cortical areas in patients with depression compared with controls.[48] Increased numbers of 5-HT$_{2A}$ receptors have been found in the platelets of patients with major depression[49,50] and suicidal patients.[51] Down-regulation of the 5-HT$_{2A/2C}$ receptors has been observed in response to SSRIs and nonselective serotonin reuptake inhibitors.[52]

Compared with control subjects, prolactin responses in patients with depression have been reported to be blunted in response to tryptophan.[53] Similarly, the prolactin response to the serotonin agonists fenfluramine and clomipramine is also blunted in patients with depression.[54,55] These results suggest a dysfunction in the 5-HT$_2$ receptor, but whether this is presynaptic or postsynaptic is unclear; although, since normal endocrine responses to *m*-chlorophenylpiperazine have been observed, any lesion may be presynaptic.[56]

Adrenoceptors

The presynaptic α_2-adrenoceptors are autoreceptors that modulate the release of norepinephrine. Studies on postmortem tissue have suggested that the density and affinity of the α_2-adrenoceptors are increased in the frontal cortex of suicide victims previously diagnosed as being depressed.[57,58] There is some evidence that the type of α_2-adrenoceptor is altered.[59,60] Changes in the sensitivity of the receptor may also occur. Studies in rats indicate that chronic desipramine treatment decreases the sensitivity and results in changes in the release of norepinephrine.[61] Charney and coworkers[62] have reported that the autoreceptors may be supersensitive in depression and the sensitivity is reduced on administration of desipramine.

Platelets have also been used as a model to investigate the effects on the α_2-adrenoceptor. Using the α_2-adrenoceptor agonist clonidine, changes in density and sensitivity have been investigated but results have been

inconsistent, with evidence for increases,[63] decreases,[64] or no change[65] in the receptor density. Similarly, antidepressants have been reported to reduce[31] or have no effect on[66] the number of receptors.

Clonidine-stimulated growth hormone secretion was found to be lowered in patients with major depression[67] and those with a history of suicide attempts[68] compared with controls, implying a reduced sensitivity, and it has been suggested that this lowered secretion may be a useful marker of potential suicidal behavior.[68]

Other changes in receptor function have also been used as a marker by which to study the effects of depression. Activation of the platelet α_2-adrenoceptor causes inhibition of adenylate cyclase and hence a decrease in cAMP production. This decrease is believed to mediate platelet aggregation, which has therefore been used as a model by which to measure α_2-adrenoceptor function. The results of such studies have been contradictory, suggesting both a desensitization[69] and a supersensitivity[70] of the α_2-adrenoceptor in patients with major depression.

Changes also occur in the numbers of β-adrenoceptors in tissues in patients with depression. Up-regulation of β-adrenoceptors has been found consistently in patients with depression, and their down-regulation is regarded as a marker of antidepressant efficacy.[23] An increase in β-adrenoceptor binding has been found in the frontal and prefrontal cortices of postmortem tissue of suicide victims compared with controls,[71,72] although this was not confirmed in another study.[73] β_1-Adrenoceptors have been reported to be down-regulated in rat forebrain in response to antidepressants and electroconvulsive therapy.[74,75] Lymphocytes have β-adrenoceptors and have been used as a model for neuronal β-adrenoceptor function. The number of binding sites on lymphocytes has been shown to be significantly increased in patients with depression, but to return to normal in patients who respond to treatment.[31,32,76] However, studies have been inconsistent, with others reporting decreased[77] or unchanged[78] numbers of receptors in patients with depression.

At present, therefore, there is no clear consensus on whether a specific lesion occurs in the postsynaptic norepinephrine and/or serotonin receptors, although in some patients such a lesion seems to be a distinct possibility.

SUBCELLULAR LESION

Finally, the lesion may be at the subcellular level. It could occur in any of the many components of the signaling systems and result in impaired responses within the serotonergic and/or noradrenergic systems. Changes in receptor density and affinity in response to antidepressants are likely to be a result of changes in the postreceptor signal transduction pathways and in gene expression. Chronic administration of antidepressants has been shown to provoke changes in cAMP-dependent and Ca^{2+}/calmodulin-dependent phosphorylation systems in certain areas of the brain[79–82] and, hence, may regulate the expression of neuronal proteins via nuclear transcription factors.

In addition, the cross-talk hypothesis predicts that components of the signaling pathways, in particular the G proteins,[80,83] may be common to the noradrenergic and serotonergic systems. It would therefore be predicted that those patients with an abnormality in a shared component would respond to multiple types of medication.[84]

SUMMARY

There is substantial evidence that a lesion in the norepinephrine and/or serotonin neurotransmitter systems is responsible for causing depression. The precise lesion may vary between individuals and requires further investigation in order to be able to predict the most effective antidepressant treatment for individual patients.

Drug names: amitriptyline (Elavil, Lentizol, and others), clomipramine (Anafranil and others), clonidine (Catapres and others), desipramine (Norpramin, Pertofran, and others), fluoxetine (Prozac, Fluctin), reboxetine (Vestra, Edronax, and others), trazodone (Desyrel, Molipaxin, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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