# Depression: The Case for a Monoamine Deficiency

Pedro L. Delgado, M.D.

The monoamine hypothesis of depression predicts that the underlying pathophysiologic basis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system. This hypothesized pathophysiology appears to be supported by the mechanism of action of antidepressants: agents that elevate the levels of these neurotransmitters in the brain have all been shown to be effective in the alleviation of depressive symptoms. However, intensive investigation has failed to find convincing evidence of a primary dysfunction of a specific monoamine system in patients with major depressive disorders. Understanding of the etiology of depression has been hampered by the absence of direct measurements of monoamines in humans. However, the monoamine depletion paradigm, which reproduces the clinical syndrome, allows a more direct method for investigating the role of monoamines. Results from such studies show that antidepressant responses are transiently reversed, with the response being dependent on the class of antidepressant. In contrast, monoamine depletion does not worsen symptoms in depressed patients not taking medication, nor does it cause depression in healthy volunteers with no depressive illness. In conclusion, it is clear that antidepressant agents in current use do indeed require intact monoamine systems for their therapeutic effect. However, some debate remains as to the precise role that a deficiency in monoamine system(s) may play in depression itself.
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The monoamine hypothesis of depression proposes that there is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system.[1] In the 1950s, reserpine, which depletes central stores of monoamines, was shown to induce depression. Reserpine was also shown to induce aspects of depression such as motor retardation and sedation in animal models. In contrast, the monoamine oxidase inhibitor iproniazid produced an antidepressant effect when administered to tubercular patients; iproniazid was later found to improve mood in depressed nontubercular patients.

For many years, the neurobiological basis of depression has been linked to the mechanism of action of antidepressants. Newer antidepressants that elevate levels of serotonin (5-hydroxytryptamine, or 5-HT), norepinephrine, and/or dopamine in the brain have been shown to alleviate effectively the symptoms of depression. Although there is substantial evidence to support a role for the monoamine systems in the mechanism of action of antidepressants,[2] intensive investigation has failed to find convincing evidence of a primary dysfunction of a specific monoamine system in patients with major depressive disorders.[3]

Understanding the relationship of monoamine systems to therapeutic antidepressant responses and the neurobiology of depression has been hindered by the lack of direct measurements of monoamines in humans. The monoamine depletion paradigm provides a more direct method for investigating the role of monoamines in drug action and mental illness, since the primary outcome measure is the capacity to reproduce the clinical syndrome itself.[4–6]

## INDIRECT EVIDENCE FOR THE ROLE OF MONOAMINES IN DEPRESSION

### Serotonin

Substantial indirect evidence supports the hypothesis that a dysfunctional serotonergic system may play a role in depression. Levels of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been reported to be lower than normal in the cerebrospinal fluid (CSF) of patients with depression[7]; however, this is not a consistent observation.[8] In addition, low concentrations of 5-HIAA in the CSF have been found to correlate with violent sui-

*From the Department of Psychiatry, University of Arizona College of Medicine, Tucson.*

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*Reprint requests to: Pedro L. Delgado, M.D., Department of Psychiatry, University of Arizona College of Medicine, 1501 N. Campbell Ave., Tucson, AZ 85724 (e-mail: delgado@u.arizona.edu).*

cide.[9,10] The number of serotonin transporter sites and the uptake of serotonin are both reduced in the platelets of antidepressant-naive depressed patients, a model for neuronal serotonin receptors.[11,12] Interestingly, there was no alteration in the number of transporter sites in patients with panic disorder, mania, Alzheimer's disease, fibromyalgia, or atypical depression, suggesting a specificity for major depression.[12] Chronic antidepressant treatment with imipramine or fluoxetine has been shown to produce a significant reduction (40%–50%) in serotonin transporter messenger RNA in the raphe nuclei.[13]

Several investigators have also reported an increase in the density of postsynaptic 5-$HT_2$ receptor binding sites in the frontal cortices of depressed suicide victims and unmedicated depressed patients.[14,15] These observations correlate well with recent observations of increased numbers of 5-$HT_{2A}$ and 5-$HT_2$ receptors on platelets of patients with major depression and suicidal patients, respectively.[16,17] It has been suggested that up-regulation of cortical 5-$HT_2$ receptors in depression is an adaptive response to reduced synaptic serotonin.[12]

### Norepinephrine

Although levels of the major norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) have been measured in urine, plasma, and CSF of patients with depression, there is little correlation between MHPG levels and depressive symptoms. Indeed, increased, decreased, and unchanged urinary MHPG concentrations have all been reported in depressed patients.[18–22] However, patients with low urinary MHPG levels have been reported to be responsive to imipramine treatment,[18] and patients with low urinary MHPG levels respond more robustly to treatment with tricyclic and tetracyclic antidepressants than do patients with high MHPG levels.[23–25] The binding of [$^3$H]-nisoxetine (a ligand for the norepinephrine reuptake transporter) has been reported to be significantly reduced in the locus ceruleus obtained postmortem from suicide victims and patients with depression compared with control subjects.[26] Chronic administration of desipramine has also been reported to decrease [$^3$H]-nisoxetine binding in several brain areas, including the hippocampus.[27]

Presynaptic $\alpha_2$-adrenoceptors may also play an important physiologic role in the regulation of the release of norepinephrine.[28] Enhanced autoreceptor activity and the subsequent decrease of norepinephrine could be involved in the etiology of depression: the density and affinity of $\alpha_2$-adrenoceptors are increased in the frontal cortex and, to a lesser extent, in the hypothalamus, amygdala, hippocampus, and cerebellum of depressed suicide victims.[29] In addition, an increase in the affinity and density of $\alpha_2$-adrenoceptors on isolated human platelets from depressed patients has also been reported.[30] Antidepressant drug treatment and electroconvulsive therapy are associated with a decrease in the density of $\alpha_2$-adrenoceptors and in the affinity of ligands at these receptors in platelets from depressed patients.[31] Measurement of the up-regulation of β-adrenoceptors in patients with depression has been shown to be reproducible, and their down-regulation is regarded as a marker of antidepressant efficacy.[32]

## RATIONALE FOR MONOAMINE DEPLETION STUDIES

If the underlying pathophysiology of depression is indeed a deficiency in specific central neurotransmitter systems as predicted by the monoamine hypothesis, then depletion of monoamines should have specific effects on depressive symptoms in particular groups of patients. By reducing the central levels of a particular neurotransmitter in a transient and reversible manner, we can investigate its importance in mental illness.

Since the synthesis of serotonin is entirely dependent on the availability of its precursor amino acid tryptophan, manipulation of tryptophan levels in the central nervous system will affect serotonin transmission. Tryptophan is an essential amino acid and humans must obtain it from dietary sources; therefore, it is a relatively straightforward process to deplete brain serotonin stores by administration of a tryptophan-free amino acid drink. This effect has been demonstrated in animal studies.[33,34]

The manipulation of central norepinephrine has been approached in a slightly different fashion, although the principle remains the same. The first and rate-limiting step in the synthesis of catecholamines is the conversion of tyrosine to L-3,4-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase. This step can be inhibited reversibly by the administration of α-methyl-*p*-tyrosine (AMPT), which therefore inhibits the production of norepinephrine (and dopamine).

## PREDICTIONS FOR THE RESULTS OF DEPLETION STUDIES

The indirect evidence outlined above suggests that a dysfunction in the serotonergic and/or noradrenergic systems may be implicated in the etiology of depression. Assuming the monoamine hypothesis holds true, what might we expect to observe when monoamines are depleted in humans with or without depression?

### Depressed Patients in Remission on Antidepressant Treatment

Since many current antidepressants function by inhibiting the reuptake of norepinephrine or serotonin, or both neurotransmitters, it seems straightforward to predict that depletion of serotonin with a tryptophan-free drink will exacerbate or cause a return to depressive symptoms in patients treated with selective serotonin reuptake inhibitors (SSRIs), and that treatment with AMPT will worsen

Table 1. Predictions for the Recurrence of Depressive Symptoms During Depletion Studies, Based on the Monoamine Hypothesis of Depression[a]

| Subjects | Serotonin Depletion | Catecholamine Depletion |
|---|---|---|
| Healthy | ++ | ++ |
| Depressed, no medication | + | + |
| Recovered while taking SSRI | +++ | – |
| Recovered while taking NRI | – | +++ |
| Recovered while taking NaSSA | +++ | +++ |

[a]Abbreviations: NaSSA = norepinephrine and specific serotonergic antidepressant, NRI = norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor. Symbols represent grades of response (arbitrary units).

Table 2. Observed Results of Monoamine Depletion Studies: Recurrence of Depressive Symptoms During Depletion[a]

| Subjects | Serotonin Depletion | Catecholamine Depletion |
|---|---|---|
| Healthy | – | ± |
| Depressed, no medication | – | – |
| Recovered while taking SSRI | ++++ | + |
| Recovered while taking NRI | + | ++++ |
| Recovered while taking NaSSA | ++++ | ++++ |

[a]Data from references 4, 35–43. Symbols: – = no effect, ± = mild effects in some subjects, + = 20%–25% of patients, ++++ = 50%–80% of patients.

depressive symptoms in patients taking norepinephrine reuptake inhibitors (NRIs) (Table 1). Patients who are in remission and taking an agent such as a norepinephrine and specific serotonergic antidepressant (NaSSA) that inhibits reuptake in both systems might be expected to experience an increase in depressive symptoms when either monoamine is depleted.

### Patients With Depression But Not Taking Medication

In this group of patients, the monoamine hypothesis predicts that patients would feel more depressed during monoamine depletion, although the actual change in depressive symptomatology might depend on the remaining level of functioning of the neurotransmitter system in question.

### Healthy Subjects

If a deficiency of one or other of the monoamine neurotransmitter systems underlies depression, then depletion of monoamines might be expected to induce depressive symptoms in healthy subjects.

## RESULTS OF MONOAMINE DEPLETION STUDIES

The results of monoamine depletion studies undertaken by our group are summarized in Table 2.

### Depressed Patients in Remission on Antidepressant Treatment

Our first study of the effects of tryptophan depletion showed that 14 (67%) of 21 patients responding to antidepressant medication in the 2 weeks prior to testing experienced a relapse of depressive symptoms (50% increase in Hamilton Rating Scale for Depression [HAM-D] with total score ≥ 17) within 5 to 7 hours of tryptophan depletion, but not during control treatment.[4] Symptoms were reported by the patients to be the same as those experienced prior to antidepressant therapy. Patients who had responded successfully to the relatively selective norepinephrine reuptake inhibitor desipramine were much less likely to relapse (20% relapse rate) than those who had responded to an SSRI or monoamine oxidase inhibitor (90% relapse rate). These results have been confirmed in a study of patients who were either antidepressant treatment–naive or who had previously responded successfully to treatment.[35] These patients were depleted of tryptophan in a double-blind manner after having responded for at least 2 weeks to treatment with either desipramine or fluoxetine. Six (46%) of the 13 responders to fluoxetine experienced a relapse, while only 1 desipramine responder (8%) of 13 relapsed.

In a similar study, we investigated the effects of catecholamine depletion in depressed patients randomly assigned to either desipramine or fluoxetine.[36,37] Thirteen (81%) of 16 desipramine responders relapsed during AMPT testing, whereas only 1 (6%) relapsed during testing with diphenhydramine as active control. In contrast, 4 (19%) of 21 fluoxetine responders relapsed during catecholamine depletion, as did 3 (14%) during control treatment.

We have also investigated the effects of monoamine depletion in patients maintained on treatment with mirtazapine, an antidepressant with effects on both the serotonergic and noradrenergic systems. In a crossover study, tryptophan and catecholamine depletion were equally as likely to cause relapse in these patients.[38]

### Patients With Depression But Not Taking Medication

We depleted 43 drug-free depressed patients of tryptophan in a double-blind, placebo-controlled crossover study.[39] In contrast to changes seen in patients on antidepressant treatment, there was only minimal change in the HAM-D score on the day of the test, and, on the day following the test, some patients experienced a worsening of symptoms, while others actually experienced an improvement. Also, there was no correlation between plasma tryptophan levels and change in HAM-D score on any day of the test.

We noted a similar lack of exacerbation of symptoms during catecholamine depletion in 50 drug-free depressed patients.[40] There was minimal change in mood during or after depletion, and there were no significant differences in HAM-D scores between AMPT and placebo testing.

### Healthy Subjects

Tryptophan depletion caused minimal symptoms in healthy subjects with no personal or family history of depression.[41–43]

### Monoamine Depletion and Vulnerability to Depression

In contrast to their results with healthy patients, Benkelfat et al.[41] reported that about 30% of subjects with a family history of affective disorders showed an increase in depressive symptoms during tryptophan depletion. We have investigated this effect further in a study of history-positive subjects who were currently remitted, but who were not taking any antidepressant medication.[42,43] Tryptophan depletion caused a significant increase in HAM-D score in all 12 history-positive subjects, although only 25% of the history-positive subjects actually relapsed. No significant changes in HAM-D scores in the 12 control subjects were found.

Similar results were observed in a study of women who had recovered from recurrent episodes of major depression, but who were not taking medication.[6] In the majority of subjects, tryptophan depletion induced a return of their depressive symptoms.

## DISCUSSION

The results of monoamine depletion studies in depressed patients currently on drug treatment can be interpreted as providing support for the hypothesis that depression is a dysfunction of the central neurotransmitter(s) norepinephrine and/or serotonin, and that restoration of neurotransmitter function by reuptake inhibition provides an effective method to treat depression. However, it is also clear from the depletion studies in medication-free symptomatic patients and healthy subjects that this is not the complete picture. The failure to exacerbate or precipitate depressive symptoms in these subjects implies that a simple lesion in the serotonergic and/or noradrenergic systems is unlikely to be the simple cause of depression. For instance, if the dysfunction in the monoamine system is not at the level of neurotransmitter (i.e., presynaptic), but in the ability of the neuronal system to recognize and/or use the neurotransmitter, alterations in the levels of monoamine would not affect depressive symptoms. It is well known that the response to antidepressant therapy is delayed and that improvement in mood is not observed until several days or weeks following treatment. This suggests that antidepressant effects may involve an alteration of the ability or sensitivity of the postsynaptic neurons to respond to monoamines.[3,44] Only after this had occurred would changes in the monoamine levels have any effect. Possible subcellular loci for a dysfunction of the postsynaptic receptors are discussed by Leonard (this supplement).[45]

Determination of the precise pathophysiology of depression therefore requires considerable further research. However, it seems likely that a shift of focus toward understanding the adaptive changes induced by antidepressants may yield further insights into the underlying neurobiological basis of depression.

*Drug names:* desipramine (Norpramin, Pertofram and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac, Fluctin), mirtazapine, (Remeron, Zispin, and others), reserpine (Serpasil 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.



## REFERENCES

1. Stahl SM. Basic psychopharmacology of antidepressants, part 1: antidepressants have seven distinct mechanisms of action. J Clin Psychiatry 1998;59(suppl 4):5–14
2. Heninger GR, Charney DS. Mechanism of action of antidepressant treatments: implications for the etiology and treatment of depressive disorders. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987:535–544
3. Delgado PL. Neurobiological basis of depression. Adv Biol Psychiatry 1995;1:161–214
4. Delgado PL, Charney DS, Price LH, et al. Serotonin function and the mechanism of antidepressant action: reversal of antidepressant induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 1990;47:411–418
5. Delgado PL, Moreno FA, Potter R, et al. Norepinephrine and serotonin in antidepressant action: evidence from neurotransmitter depletion studies. In: Briley M, Montgomery SA, eds. Antidepressant Therapy at the Dawn of the Third Millennium. London, UK: Martin Dunitz Ltd; 1997:141–163
6. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. Lancet 1997;349:915–919
7. Cheetham SC, Katona CLE, Horton RW. Post-mortem studies of neurotransmitter biochemistry in depression and suicide. In: Horton RW, Katona CLE, eds. Biological Aspects of Affective Disorders. London, UK: Academic Press; 1991:192–221
8. Gjerris A. Baseline studies on transmitter substances in cerebrospinal fluid in depression. Acta Psychiatr Scand 1988;78(suppl 346):1–36
9. Åsberg M, Träskman L, Thorèn P. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch Gen Psychiatry 1976;33:1193–1197
10. Brown GL, Goodwin FK. Cerebrospinal fluid correlates of suicide attempts and aggression. Ann N Y Acad Sci 1986;487:175–188
11. Healy D, Leonard BE. Monoamine transport in depression: kinetics and dynamics. J Affect Disord 1987;12:91–103
12. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin receptor. Clin Chem 1994;40:288–295
13. Lesch K-P, Aulakh CS, Wolozin BL, et al. Regional brain expression of serotonin transporter mRNA and its regulation by reuptake inhibiting antidepressants. Mol Brain Res 1993;17:31–35
14. Stanley M, Mann JJ. Increased serotonin-2 binding sites in frontal cortex of suicide victims. Lancet 1983;1:214–216
15. Yates M, Leake A, Candy JM, et al. 5-$HT_2$ receptor changes in major depression. Biol Psychiatry 1990;27:489–496
16. Bakish D, Cavazzoni P, Chudzik J, et al. Effects of selective serotonin reuptake inhibitors on platelet serotonin parameters in major depressive disorder. Biol Psychiatry 1997;41:184–190
17. Hrdina PD, Bakish D, Ravindran A, et al. Platelet serotonergic indices in major depression: up-regulation of 5-$HT_{2A}$ receptors unchanged by antidepressant treatment. Psychiatry Res 1997;66:73–85
18. Maas JW, Fawcett JA, Dekirmenjiam H. Catecholamine metabolism, depressive illness and drug response. Arch Gen Psychiatry 1972;26:252–262
19. Schildkraut JJ, Orsulak PJ, Schatzberg AF, et al. Toward a biochemical classification of depressive disorders, I: differences in urinary excretion of MHPG and other catecholamine metabolites in clinically defined subtypes of depressions. Arch Gen Psychiatry 1978;35:1427–1433
20. Potter WZ, Muscettola G, Goodwin FK. Sources of variance in clinical studies in MHPG. In: Maas JW, ed. MHPG: Basic Mechanisms and Basic Psychopathology. New York, NY: Academic Press; 1983:145–165

21. Muscettola G, Potter WZ, Pickar D, et al. Urinary 3-methoxy-4-hydroxyphenyl-glycol and major affective disorders. Arch Gen Psychiatry 1984;41:337–342
22. Schatzberg AF, Samson JA, Bloomingdale KL, et al. Toward a biochemical classification of depressive disorders, X: urinary catecholamines, their metabolites and D-type scores in subgroups of depressive disorders. Arch Gen Psychiatry 1989;46:260–268
23. Hollister LE, David KL, Berger PA. Subtypes of depression based on excretion of MHPG and response to nortriptyline. Arch Gen Psychiatry 1980; 37:1107–1110
24. Schatzberg AF, Rosenbaum AH, Orsulak PJ, et al. Toward a biochemical classification of depressive disorders, III: pre-treatment urinary MHPG levels as predictors of response to treatment with maprotiline. Psychopharmacology 1981;75:34–38
25. Maas JW, Koslow SH, Katz MM, et al. Pre-treatment neurotransmitter metabolite levels and response to tricyclic antidepressant drugs. Am J Psychiatry 1984;141:1159–1171
26. Klimek V, Stockmeier C, Overholser J, et al. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 1997;17:8451–8458
27. Bauer ME, Tejani-Butt SM. Effects of repeated administration of desipramine or electroconvulsive shock on norepinephrine uptake sites measured by ($^3$H)nisoxetine autoradiography. Brain Res 1992;582:208–214
28. Langer SZ. Presynaptic regulation of the release of catecholamines. Pharmacol Rev 1981;32:337–362
29. Meana JJ, Barturen F, García-Sevilla JA. Alpha$_2$-adrenoceptors in the brain of suicide victims: increased receptor density associated with major depression. Biol Psychiatry 1992;31:471–490
30. Piletz JE, Halaris A, Saran A, et al. Elevated $^3$H-para-amino-clonidine binding to platelet purified plasma membranes from depressed patients. Neuropsychopharmacology 1990;3:201–210
31. García-Sevilla JA, Padro D, Giralt MT, et al. Alpha$_2$-adrenoceptor-mediated inhibition of platelet adenylate cyclase and induction of aggregation in major depression: effect of long-term cyclic antidepressant drug treatment. Arch Gen Psychiatry 1990;47:125–132
32. Leonard BE. The role of noradrenaline in depression: a review. J Psychopharmacol 1997;11(4, suppl):S39–S47
33. Moja EA, Cipollo P, Castoldi D, et al. Dose-response decrease in plasma tryptophan and in brain tryptophan and serotonin after tryptophan-free amino acid mixtures in rats. Life Sci 1989;44:971–976
34. Young SN, Ervin FR, Pihl RO, et al. Biochemical aspects of tryptophan depletion in primates. Psychopharmacology 1989;98:508–511
35. Delgado PL, Miller HL, Salomon RM, et al. Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. Biol Psychiatry 1999;46:212–220
36. Delgado PL, Moreno FA, Buonopane A, et al. Catecholamine depletion in desipramine and fluoxetine responders. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 7, 1996; New York, NY. Abstract NR334:157
37. Miller HL, Delgado PL, Salomon RM, et al. Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. Arch Gen Psychiatry 1996;53:117–128
38. Delgado PL, Moreno FA, Gelenberg AJ, et al. Sequential catecholamine and 5-HT depletion in mirtazapine-treated depressives. In: Society of Biological Psychiatry 53rd Annual Scientific Convention and Program; May 27–30, 1998; Toronto, Ontario, Canada. MS 973385
39. Delgado PL, Price LH, Miller HL, et al. Serotonin and the neurobiology of depression: effects of tryptophan depletion in drug-free depressed patients. Arch Gen Psychiatry 1994;51:865–874
40. Miller HL, Delgado PL, Salomon RM, et al. Effects of alpha-methyl-para-tyrosine (AMPT) in drug-free depressed patients. Neuropsychopharmacology 1996;14:151–158
41. Benkelfat C, Ellenbogen MA, Dean P, et al. Mood-lowering effect of tryptophan depletion: enhanced susceptibility in young men at genetic risk for major affective disorders. Arch Gen Psychiatry 1994;51:687–697
42. Moreno FA, Delgado PL, McKnight K, et al. Tryptophan depletion: a potential predictor of depressive episodes. Presented at the 26th Annual Meeting of the Society for Neuroscience; Nov 21, 1996; Washington, DC. Abstract 811.9
43. Moreno FA, Gelenberg AJ, Heninger GR, et al. Tryptophan depletion and depressive vulnerability. Biol Psychiatry 1999;46:498–505
44. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry 1997;54:597–606
45. Leonard BE. Evidence for a biochemical lesion in depression. J Clin Psychiatry 2000;61(suppl 6):12–17



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