The Role of Dopamine and Norepinephrine in Depression and Antidepressant Treatment

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Most antidepressants in use today are descendants of the monoamine oxidase inhibitor iproniazid and the tricyclic agent imipramine. These agents were both originally developed for other indications but then were serendipitously determined to have antidepressant effects. Elucidation of the mechanisms of action of these first antidepressants, along with those of reserpine and amphetamine, led to the monoamine theories of depression. Through the past several decades, approaches undertaken to clarify the roles of the neurotransmitters norepinephrine, dopamine, and serotonin in depression have included animal studies, human biological and postmortem studies, inferences drawn from antidepressant drug actions, and challenge or depletion studies; most recently, brain imaging studies have proved to be especially informative. This research has identified novel potential targets, with the goal of developing new antidepressant drugs with better efficacy and faster onset of action than current "gold-standard" treatments. *(J Clin Psychiatry 2006;67[suppl 6]:3–8)*

The roles of norepinephrine (NE) and dopamine (DA) in depression are very much entwined, with each other as well as with the mechanisms of action of antidepressants. Research into the roles of these neurotransmitters goes back over the past 50 years.[1] Approaches undertaken to elucidate their roles in depression include animal studies, human biological and postmortem studies, and inferences drawn from drug actions observed in antidepressant studies.[2] Biological and postmortem studies have yielded few definitive data, but some data provide glimpses of the role of certain metabolites.

Investigations of cerebrospinal fluid metabolites such as the DA metabolite homovanillic acid in depression reveal low levels in some forms of the disorder. Reduced whole-body NE turnover has been noted in bipolar depression, suggesting a central deficiency of NE activity. Lower-level evidence exists from indirect measures of NE and DA activity; one such is from apomorphine, a DA agonist that releases growth hormone, an effect that is blunted in some studies of depression.[2] Other forms of challenge for growth hormone may also be blunted in depression, and thus growth hormone may not be a specific marker for DA. Brain imaging as a means of studying the role of DA in depression has advanced rapidly in recent years, with several groups finding evidence for reduced synaptic dopamine using PET and SPECT tracers that are sensitive to synaptic dopamine levels. Yet another approach has been to make inferences about DA and NE in depression based on patient response to antidepressant drugs. Amphetamine-induced mania, for example, has been well-recognized and probably relates to increased release of dopamine plus or minus norepinephrine. Other dopamine-releasing stimulants, especially cocaine, have also been shown to induce mania. The antihypertensive drug reserpine was used in studies to model depression in humans.[3] Clonidine, another antihypertensive agent that reduces NE in a different way, can cause depression as well. Additionally, there is a vast body of evidence that various antidepressants affect NE and, to a lesser extent, DA, particularly the tricyclic antidepressants (TCAs) and some derivatives.

ANIMAL STUDIES

A substantial body of evidence based on animal models of depression exists. One well-studied model involves an induced state of helplessness in rats, a model associated with quantifiable symptoms such as loss of body weight and change in grooming habits. Evidence suggests that the deficiency of behaviors is associated with an increase in presynaptic inhibitory α_2 receptors leading to a secondary decrease in NE release.[4] Drugs that block α_2 receptors and increase NE release have been shown to work in learned helplessness models. Other models have used the synthesis inhibitor α-methylparatyrosine (AMPT) to block NE synthesis and produce a depressionlike state in animals.

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Reserpine and Depletion of Norepinephrine

Reserpine is an antihypertensive agent with a side effect of behavioral and motor depression. Some evidence suggests that reserpine is associated not only with behavioral depression but also with an increase in the number of α_2 receptors, which in turn decreases NE release. In fact, the depletion of amines that occurs with reserpine treatment has been used as a primary screening test to define potential antidepressants, since antidepressant agents have been shown to antagonize reserpine-induced motor depression.[3] One criticism of the reserpine test is that it is circular in nature—it reveals only drugs that work in the reserpine test, so novel agents with actions independent of amines would not work in this test.

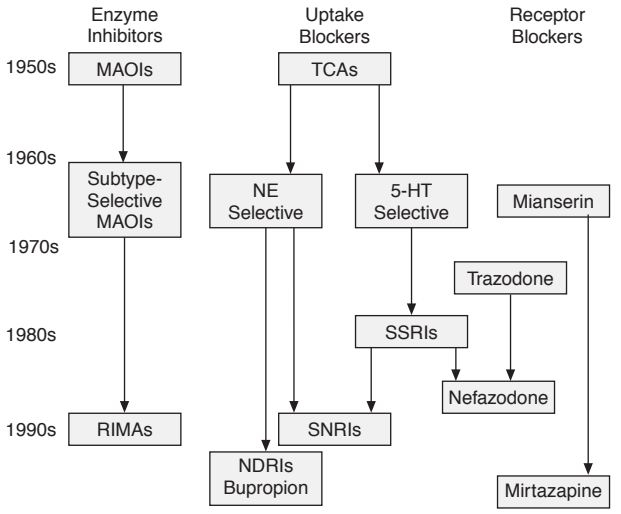
Dopamine Research

The field of research involving DA and depression has been of great interest for the last 10 years. Willner et al.[5] developed a chronic stress model in rats in an attempt to model human depression. In this chronic stress model, animals were given a repeated series of minor stresses via changes in their environment, none of which by themselves would cause any perturbation of behavior. When this collection of stresses was applied for several days, it led to mild or moderate depression. Study animals became less active and experienced decreased appetitive (hedonic) drive, as measured by saccharin solution intake, an effect that was reversible with standard antidepressants—both TCAs and selective serotonin reuptake inhibitors (SSRIs). This decrease in appetitive drive has been suggested to be due to DA-receptor subfunction because of the considerable evidence implicating the DA system in fundamental drives such as appetite. Electroconvulsive therapy (ECT) was also shown to reverse the modeled depression[5] and is known to increase dopamine function in rats and humans (see below).

There are 2 main DA systems that appear to play complementary roles in depression. Symptoms like psychomotor retardation may reflect subfunctioning of the substantia nigra basal ganglia motor system. A second parallel system extends from the ventral tegmental area into the ventral striatum—the ventral part of the basal ganglia or the nucleus accumbens—and then up into the prefrontal cortex where it is involved in attention and planning. In the nucleus accumbens, DA release seems to be important in learned associations, especially relating to pleasurable outcomes. One theory of depression in humans based on animal research is that individuals do not experience proper reward from normal social interaction because of DA deficiency in this brain region.[4] In these individuals, the brain does not make the appropriate association that the interaction is actually rewarding; therefore, this reward system may be a target for antidepressant activity.

In contrast to serotonin (5-HT) or NE projections, DA projections in the frontal cortex are much more localized.

Figure 1. Evolution of Antidepressants[a]



[a]Adapted with permission from Slattery et al.[2]
Abbreviations: 5-HT = serotonin, MAOI = monoamine oxidase inhibitor, NDRI = norepinephrine-dopamine reuptake inhibitor, NE = norepinephrine, RIMA = reversible inhibitor of monoamine oxidase type A, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

While NE and 5-HT are found throughout the brain, DA is found only in the prefrontal cortex. The innervation of the DA projection in the prefrontal cortex is low in terms of DA terminals, but it is a very stress-sensitive system, so it shows a large increase in activity compared with the basal ganglia system in response to stress. One theory of how stress might lead to depression is that this system becomes "burned out" by chronic stress, leading to a relative deficiency of DA in the region, which then leads to depression.

EVOLUTION OF ANTIDEPRESSANT TREATMENTS

Pharmacologic Agents

The first of the antidepressants were discovered initially by serendipity, but some of the major advances in the science of neurotransmitters have resulted from subsequent attempts to understand how antidepressants work. The monoamine oxidase inhibitor (MAOI) iproniazid and the TCA imipramine were being developed for other indications (an antitubercular drug and antihistamine/antipsychotic, respectively) but were shown to have antidepressant actions, empirical discoveries derived from astute clinical observation (Figure 1).[1,2] In the 1960s, researchers quickly discovered that the MAOIs block the metabolism of NE and 5-HT and increase levels of DA, NE, and 5-HT in brain samples.[6,7]

The action of TCAs was more difficult to understand. In the 1960s, Axelrod et al.[8] discovered NE uptake. While attempting to determine how imipramine worked, researchers found that the brain deals with most neuro-

transmitters by taking them back into terminals or glial cells. Soon thereafter, researchers realized imipramine blocked not only NE uptake,[6,8,9] but also 5-HT uptake.[10–12] This discovery led to the development of SSRIs.

Antidepressant research further evolved in the 1970s as a result of understanding mechanisms of action. The 2 subtypes of monoamine oxidase became easy to target with drugs like pargyline (a monoamine oxidase-A [MAO-A] selective drug) and selegiline (a monoamine oxidase-B [MAO-B] selective drug) being discovered. Selegiline, developed initially as a DA-sparing agent and a possible neuroprotective agent in Parkinson's disease,[13,14] has recently garnered interest as a possible alternative antidepressant treatment, and a patch preparation[15] has recently been approved by the U.S. Food and Drug Administration for the treatment of depression.

Once the mechanisms of actions of the TCAs were unraveled, a range of tricyclic drugs evolved. The first new agents were NE selective (desipramine, protriptyline, nortriptyline, lofepramine), and although they had a tricyclic structure, blocked only NE uptake.[1] Zimelidine, the first of the 5-HT uptake inhibitors, in many ways revolutionized the field.[16] The SSRIs (fluvoxamine, paroxetine, fluoxetine, sertraline, and citalopram, among others) have been vastly successful in terms of their improved safety and tolerability profile over the TCAs.[1] But not all of these agents proved to be as safe as they were effective, and several were withdrawn from the market due to adverse events. For example, nomifensine, a dopaminergic agent with some NE-uptake–blocking properties, was withdrawn due to immune hemolytic anemia,[17] and nefazodone, a weak SSRI and potent 5-HT_2 receptor antagonist, was withdrawn due to hepatitis. Bupropion is the only proven antidepressant currently in use that acts through a direct dopaminergic mechanism with some action to enhance noradrenergic function as well.[1]

The most recent development in antidepressants is the class known as serotonin-norepinephrine reuptake inhibitors (SNRIs).[1] These drugs (venlafaxine, milnacipran, and duloxetine) have the ability to block both 5-HT and NE uptake, so they act like the first TCAs but without the unwanted adverse effects of histaminergic, α_1, and cholinergic blockade. These drugs have a marked clinical utility at present. There seem to be some clinical differences between the actions of the SNRIs and the SSRIs. For example, the SSRI escitalopram is enormously selective and is clearly only working through 5-HT reuptake inhibition, whereas venlafaxine, at least in doses over 150 mg/day, has a significant noradrenergic component. However, while the primary pharmacology of most antidepressants is relatively well understood, the final mode of action of these drugs is still unclear to some extent (see below).

Electroconvulsive Therapy

ECT was initially studied as a treatment for depression based on earlier work with other convulsants, especially the γ-aminobutyric acid blocker pentylenetetrazole.[18] Since the 1970s, much effort has been put into understanding the commonalities of ECT and antidepressants in an attempt to find the final common pathway. One of the interesting findings about ECT is that, much more than any other antidepressant treatment, ECT increases DA function.[19] Data from the 1970s and 1980s are plentiful, particularly on increasing the responsiveness of rats to L-dopa (for review, see Nutt and Glue[20]). One theory summarizing the possible antidepressant mechanism of ECT suggests that ECT initially enhances DA receptor function,[20] then synaptic NE is increased, most likely owing to changes in α_2 receptors. Toward the end of a course of ECT, i.e., after 6 to 8 seizures, 5-HT function is enhanced. This stepwise process of enhancing amine function with ECT may provide clues as to why drugs affecting NE or DA may have quicker onset of action than do serotonergic drugs.

TESTING THEORIES OF ANTIDEPRESSANT ACTION

One method for determining whether antidepressants work through changing amines or through changing receptors is by utilizing hormonal responses to apomorphine challenges to estimate dopamine receptor function.[3,21] The noradrenergic system may also be challenged using drugs like clonidine.[22,23] Such studies have a limitation in that they use proxy measures of hormones that may be under the control of other neurotransmitters and hormones. Two other methods for determining how antidepressants work are amine-depletion studies and brain imaging.

The principle involved in amine depletion is that the production of amines in the brain is determined by the availability of the precursor. In the case of DA and NE, the precursor tyrosine is converted to L-dopa, then to DA or to NE in some neurons. The key enzyme involved is tyrosine hydroxylase. If the availability of tyrosine is increased, additional L-dopa is not produced because the enzyme is saturated. But if tyrosine is decreased, in some circumstances, the synthesis of L-dopa may be reduced, thus reducing the availability of DA. In studies, reduced tyrosine levels are accomplished through a 1-day, low-protein diet, and the next day, the subject is given a drink containing amino acids. These amino acids compete for the same uptake site across the blood-brain barrier as tyrosine. With plentiful amines and little tyrosine, the access of tyrosine to the brain is reduced so that tyrosine and DA levels fall. This effect has been demonstrated both in animal and human studies.[24–26]

In rats, it has been shown that DA synthesis in brain may be markedly reduced through this approach.[5,27] Research in humans has demonstrated that tyrosine depletion reduced the effect of stimulants, such as amphetamine.[28] Interestingly, tyrosine depletion did not cause depressive relapse in patients who had recovered predominantly on SSRI

treatment or who were drug-free.[29,30] It is not known whether tyrosine depletion would cause a relapse of depression in patients who have recovered with a dopaminergic agent, similar to tryptophan depletion causing a relapse of depression in patients treated with a serotonergic agent.[31–33]

Further research has showed reduction of manic symptoms using this tyrosine depletion approach,[34] and there has been some interest in developing this diet as a way of controlling low-grade mania.[35] Strangely, even though DA is a precursor of NE, and DA is depleted by tyrosine, NE levels are not reduced. Currently, the only proven way of reducing NE levels is by blocking synthesis through blocking tyrosine hydoxylase directly with AMPT.[2] Research has showed approximately two thirds of patients treated with the NE reuptake inhibitor desipramine experienced a relapse when given AMPT, but it had very little effect on SSRI-treated patients.[36] Interestingly, mirtazapine was sensitive both to AMPT and tryptophan depletion.[37] It is not known whether bupropion is sensitive to NE or DA depletion.

BRAIN IMAGING

In recent years, the most technical advances in neurotransmitter research have been seen in the area of brain imaging. The NE system is not yet amenable to study with imaging tools, but studies utilizing DA tracers and positron emission tomography (PET) or single-photon emission computed tomography (SPECT) scans have permitted the imaging of a number of components of the DA system.[38] One unexpected finding showed that smokers have very low availability of MAO-B in the brain compared with nonsmokers.[39,40] Substances in tobacco smoke block the enzyme. This forms the basis of one theory as to why smoking lifts mood, and smoking cessation lowers mood; additionally, it may explain why long-term smoking protects against Parkinson's disease. The antidepressant effect of smoking may possibly be mediated through blocking MAO-B. Smokers also have less MAO-A available in the brain, which suggests that smoking blocks MAO-A as well.

PET and SPECT imaging of tracers that bind to the DA transporters (DATs) shows high density of these transporters in the basal ganglia. In depressed patients, DAT density is lower than that in control subjects. There is a high density of dopamine-2 (D_2) receptors in exactly the same brain regions as the DATs. DA is released from the terminals and acts across the synapse on the D_2 receptor.

As SPECT tracers of dopamine transporters have become available, interest in the presynaptic DA system has increased. One study found a relative increase in transporter binding in depressed patients compared with normal controls,[41] exactly the opposite of that seen with stimulant abusers. This result could imply that there are more transporters in depression, and therefore, more DA uptake. Another possibility is that there is competition for DA between the synaptic cleft and the transporter binding tracer, resulting not in more binding but rather in less DA. The relative deficiency of DA in the synapse may lead to change in mood that may improve with antidepressant treatment.[42]

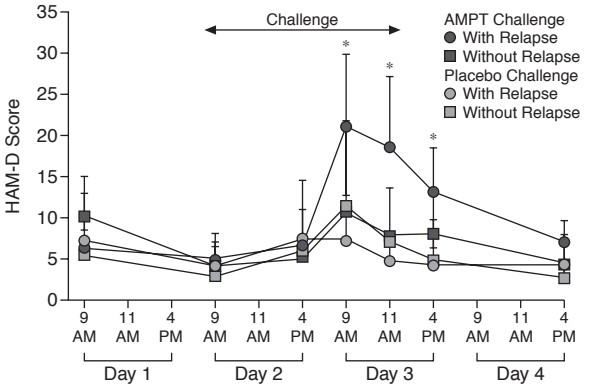
Dopamine-2 postsynaptic receptors may be labeled with the tracer [^{11}C]raclopride.[38] Until recently, there was a reasonable degree of agreement that DA receptor numbers were elevated in depression, arguably consistent with a reduction of DA in the synapse, because the binding of raclopride is sensitive to endogenous DA due to the fact that the affinity of [^{11}C]raclopride is similar to that of DA.[38,43–46] [^{11}C]Raclopride has been used in studies to estimate DA levels in the synapse, one theory being that when there is a low level of DA in the synapse, there is an increase in [^{11}C]raclopride binding. If a stimulant or antidepressant is used to increase DA in the synapse, there is relatively less [^{11}C]raclopride binding, so elevations of [^{11}C]raclopride binding are consistent with reduced levels of DA in the synapse.

A more recent study[47] looked at the ability of amphetamine to release DA to determine if there was a difference in depression. This same approach used in schizophrenic patients showed a relative overrelease of DA in response to the administration of amphetamine.[48] The data in depression showed little difference in the ability of amphetamine to displace DA in healthy control subjects and in patients with major depression. These findings perhaps suggest there is no fundamental abnormality of the D_2 system or in presynaptic DA in depression.

A peculiar paradox is that DA blockers—particularly D_2 blockers—may cause depression in schizophrenia, which supports the view that the deficiency of DA leads to depression. However, other studies have suggested that DA blockers may yield antidepressant action, particularly low-dose flupenthixol[49] or sulpiride,[50] or in cases of treatment-resistant depression in which atypical antipsychotics were added to antidepressant treatment.[51] Aripiprazole, a DA partial agonist, also has a possible antidepressant effect.[52] The basis of these anomalies remains unknown but may reflect differential sensitivity to blockade in different dopamine pathways, or differential actions on presynaptic versus postsynaptic receptor actions.

Relatively few brain-imaging studies on NE and depression have been published. One such study[53] attempted to determine exactly where in the brain NE works to lift depression. Eighteen patients who had recovered from depression on desipramine treatment were given AMPT to reduce NE synthesis in the brain and were evaluated with the Hamilton Rating Scale for Depression (HAM-D). Imaging studies were then performed. After receiving AMPT, 11 patients relapsed, according to evaluation with the HAM-D. PET imaging of regional brain metabolic activity with fluorodeoxyglucose in these patients showed a significant decrease in metabolism in the orbital frontal cortex, the lateral prefrontal cortex, and the thalamus as a

Figure 2. Norepinephrine and Depression: AMPT and Regional Blood Flow Changes[a]



[a]Reprinted with permission from Bremner et al.[53] Patients were divided into those with and without an AMPT-induced depressive relapse. In patients with AMPT-induced relapse, AMPT, but not placebo, resulted in an increase in depressive symptoms on day 3.
*p < .001 vs. placebo.
Abbreviations: AMPT = α-methylparatyrosine, HAM-D = Hamilton Rating Scale for Depression.

consequence of the relapse in mood, suggesting the possibility that a noradrenergic-regulated circuit underpins depression (Figure 2).

Recent imaging research is actively seeking methods by which NE may be measured in the human brain. In order to accomplish this, tracers sensitive to NE—like [^{11}C]raclopride is sensitive to DA—are being developed. One such tracer is 2-fluoro-ethoxy-idazoxan, an antagonist that is very selective and sensitive to endogenous NE.[54] Three different treatments, D-amphetamine, BU224 (an imidazoline compound), and selegiline, were all shown to reduce the tracer binding potential in this animal study.[54] This effect was assumed to have resulted from an increase in receptor occupancy by the endogenous neurotransmitter (i.e., an increase in extracellular NE).

On a final note, new Parkinson's disease research may have implications in terms of understanding the neurobiology of mood. This line of research involves injecting infusions of glial-derived nerve factor into the basal ganglia of patients with Parkinson's disease in an attempt to impact DA function in the brain by regrowing DA terminals.[55] Baseline imaging shows the relative deficiency of DA measured by the turnover of fluorodopa that was to some extent restored by growth factor infusion. Moreover, when [^{11}C]raclopride binding was used to estimate dopamine release following amphetamine, enhanced release was found, which further supports the view that the growth factors are producing more dopamine nerve terminals. Interestingly, mood as well as motor function has been shown to be improved by this method, which might suggest a direct effect of increased dopamine to improve mood. Further research is ongoing.

CONCLUSION

The body of evidence supporting NE and DA dysfunction in depression, while not yet definitive, is nonetheless growing. Many possibilities for new research are now available, particularly imaging and neurotransmitter depletion studies. Existing data clearly demonstrate the efficacy of noradrenergic agents as antidepressant treatments. Some evidence exists supporting the efficacy of dopaminergic agents in depression, although these data are relatively weak compared with data for the efficacy of serotonergic agents. By targeting the neurotransmitters involved in depression, it is the hope that more effective treatments may be developed, ultimately improving the quality of care for patients with depression.

REVIEW QUESTION

Mr. A is a 39-year-old midlevel executive in a multinational company. For the last year, he has been underperforming at work on account of depression that had partially responded to sertraline, but he was still disabled even when the dose was increased to 200 mg/day. He reported particular problems with energy, drive, and concentration, especially in the mornings. He was switched to venlafaxine, 75 mg/day, which was increased to 250 mg/day with slight improvement in mood, although he was still underperforming at work and feared for his job. When a colleague left, he was given extra responsibility at work, which led to worsening of depression and anxiety, which in turn led to his taking 1 month of sick leave.

In your opinion, what should be the next step in Mr. A's treatment?

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), citalopram (Celexa and others), clonidine (Catapres, Duraclon, and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil, Pexeva, and others), protriptyline (Vivactil), reserpine (Serpalan and others), selegiline (Eldepryl, Emsam, and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole is not approved by the U.S. Food and Drug Administration for the treatment of depression.

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