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Dopamine and Depression

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1. INTRODUCTION

Monoamine-based theories of major depressive disorder (MDD) have dominated thinking in biological psychiatry for over 40 yr. These theories were largely grounded on the principle of "reverse engineering." In this case, the demonstrable effects of "first generation" antidepressants (e.g., tricyclics, such as imipramine) on the reuptake of norepinephrine and serotonin *(1,2)*, and the observation that drugs depleting these biogenic amines lower mood *(3)*.

A role for dopamine in depression was first hypothesized in the mid- to late-1970s *(4,5)*, well after the link between norepinephrine, serotonin, and depression had been established. In addition to the difficulties inherent in promulgating a new hypothesis, interest in exploring the role of dopamine (and other transmitters) in MDD was dampened by the demonstration that selective serotonin reuptake inhibitors (SSRIs) were effective antidepressants. The commercial success of the SSRIs focused attention on the serotonergic synapse in the etiology of MDD and as a target for the development of new antidepressants. Despite several seminal publications appearing in the early 1980s (e.g., refs. *6* and *7*), studies to explore the role of dopamine in MDD were, with few notable exceptions, considered out of fashion. However, the contribution of anhedonia to depressive symptomatology, and the recognition that dopaminergic transmission is critical to reward and motivational processes, refocused attention on the role of the dopaminergic synapse in MDD. Although it is naive to view a single transmitter as responsible for the constellation of symptoms that comprise MDD (*see* Chapter 10; *see* refs. *8* and *9* for review), this chapter overviews preclinical and clinical evidence linking dopamine and the pathways subserved by this transmitter to MDD and antidepressant action.

2. "HYPODOPAMINERGIA" IN MDD

There is an extensive literature dating back more than 30 yr *(10)* that links activation of mesocorticolimbic dopaminergic pathways to rewarding events and incentive-driven, goal-oriented behaviors (reviewed in refs. *11* and *12*; *see* Chapter 14). It is this literature that provides the framework linking dopaminergic pathways to MDD. Anhedonia (the inability to experience pleasure) and diminished interest in all (or almost all) activities are central to a diagnosis of MDD. The link between anhedonia and dopaminergic pathways

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stems from the "dopamine hypothesis of reward" *(6)*. Wise *(6)* reported that neuroleptics delayed impairment of operant reinforcement maintained by diverse reinforcers, including food, water, drugs, and intracranial self-stimulation. Wise *(6)* concluded that neuroleptics (and by implication blockade of dopamine receptors) specifically impair primary reinforcement, and that this action is dissociable from an effect on performance. Wise *(6)* viewed this effect of neuroleptics as impairing the pleasurable effects of rewarding stimuli (i.e., anhedonia), and hypothesized that the hedonic properties of reward are effected through dopamine.

Although the dopamine hypothesis of reward has been refined and reinterpreted over the past two decades (e.g., refs. *13* and *14*), there is general agreement that activation of mesocorticolimbic dopaminergic pathways is pivotal in the selection and orchestration of both goal-directed behaviors and reward-related learning. An in-depth treatment of this topic is provided by Beninger and Gerdjikov (*see* Chapter 14).

An animal model of an affective disorder such as depression cannot be fully validated. Nonetheless, the chronic mild stress (CMS) paradigm developed by Willner and colleagues exhibits considerable face, construct, and predictive validity (reviewed in ref. *15*). In this model, rats are exposed to daily sessions of uncontrollable, inescapable stressors (e.g., cage tilt, stroboscopic light, wet bedding). The primary behavioral expression of this model, subsensitivity to a reward (e.g., the availability of a palatable solution of sucrose/saccharin; the opportunity to respond for intracranial self-stimulation [ICSS]), may reflect a diminished ability to experience pleasure. Several weeks of CMS are required to elicit this apparent subsensitivity to reward, and antidepressants, administered over a period of weeks, can reverse this phenomenon (reviewed in refs. *15* and *16*). Several studies have documented that the CMS model alters mesocorticolimbic dopaminergic pathways to produce a functional hypodopaminergia. Thus, Papp et al. *(17)* reported a reduction in radioligand binding to D2/D3 receptors in the nucleus accumbens (but not the striatum) of rats subjected to CMS. This effect was reversed by chronic administration of imipramine. Expression of mRNA-encoding D2 receptors is also reduced following an extended period of CMS *(18)*. This reduction is observed in the shell and core of the accumbens, as well as in lateral aspects of the caudate. CMS also appears to reduce expression of D2 mRNA-in cell body-rich areas including the substantial nigra and lateral (but not medial) aspects of the ventral tegmentum. By contrast, expression of mRNA-encoding D1 receptors was largely unaffected by CMS. These studies complement a more extensive literature describing the effects of antidepressants on dopaminergic pathways detailed in Subheading 3.

CMS has also been reported to blunt the rewarding (evaluated in a conditioned place preference paradigm) and motor stimulant properties of quinpirole, a D2/D3 agonist *(19)*. The latter observation should be viewed in the context of a large body of evidence (described in Subheading 3) that chronic (but not acute) antidepressant treatments *enhance* locomotor responses to dopamine agonists, including quinpirole. CMS does not appear to alter basal dopamine content in dialysates from the nucleus accumbens *(20)*. At face value, this would seem at variance with a clinical literature indicating decreased levels of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) of depressed individuals. However, in response to presentation of rewarding stimuli, dopamine levels increase in the nucleus accumbens (and prefrontal cortex) (reviewed in ref. *14*). This increase in dopamine, elicited by presentation of palatable food, is *blunted*

(in both regions) in rats subjected to CMS, and restored by chronic treatment with desipramine *(20)*. Further, in control rats, the response to an aversive stimulus (in this case, tail pinch) is a *reduction* in dopamine with a probe implanted in the nucleus accumbens. In rats subjected to CMS, there is a significant *increase* in dopamine output. These latter findings may be viewed as consistent with clinical studies indicating there is a reduction in dopamine turnover in MDD.

Much of the evidence for a reduced turnover of dopamine in depressed individuals has been in the literature for more than a quarter century (reviewed in ref. *7*). This evidence is grounded on reports that levels of HVA, the major metabolite of dopamine, are lower in CSF of depressed individuals compared to controls. This interpretation is predicated on the assumptions that both dopamine reuptake and CSF flow are unchanged in these depressed individuals, with HVA concentrations proportional to dopamine release. Many, but not all studies report (reviewed in refs. *7* and *21*) this reduction in depressed individuals. A more consistent picture emerges in individuals administered probenecid, a drug that blocks acid transport out of the CSF. Reduced CSF HVA levels have been reported in the majority of depressed individuals in these studies. However, interpretation of these data as they relate to a hypodopaminergia in MDD is not straightforward. Most CSF HVA likely emanates from the caudate nucleus, owing to both its size and relative proximity to the ventricular system. Thus, alterations in CSF HVA levels are more likely to reflect changes in activity of nigrostriatal rather than mesocorticolimbic DA function. This interpretation is consistent with: (1) reports that low CSF HVA levels are associated not only with depression, but also with Parkinson's and Alzheimer's disease *(22)*; (2) that CSF HVA levels are generally elevated in mania (reviewed in ref. *23*), and (3) the observation that CSF HVA levels are lowest in patients with marked psychomotor retardation (reviewed in ref. *7*). *In toto*, these data are consistent with the hypothesis that CSF HVA levels may more accurately reflect motor activity rather than depressed mood. Nevertheless, several double-blind studies indicate that among depressed subjects who improved following antidepressant treatment, those patients with the lowest levels of CSF HVA levels (and by inference, the most profound hypodopaminergia) responded best. Jimerson and Post (reviewed in ref. *24*) reported a significant negative correlation ($r = -0.66$; $p < 0.05$) between these measures. The antidepressants used in both of these studies are dopaminergics, piribedil (a dopamine agonist), and nomifensine *(25)*, a dopamine/norepinephrine reuptake blocker *(26)*. Although the number of patients in both studies were small, Van Scheyen et al. *(25)* did not observe a similar relationship between CSF HVA levels and individuals responding to chlomipramine.

Bowden et al. *(27)* reported no significant differences in dopamine and HVA concentrations in caudate, putamen, and nucleus accumbens in suicide victims with a documented history of depression compared to controls, although there was a trend for HVA concentrations to be lower in suicides. Lower concentrations of the dopamine metabolite dihydroxyphenylacetic acid (DOPAC) were reported in caudate nucleus of those suicides free of antidepressants. These data are consistent with a decreased turnover of dopamine in depression in view of reports of either no change in ligand binding to dopamine transporters in suicide victims *(28)* or a decrease in transporter binding "potential" (using the position emission tomography [PET] ligand, [^{11}C]RTI-32) in the striatum of depressed individuals *(29)*.

Although these clinical studies may be viewed as consistent with a hypodopaminergia in MDD, this association is far from causal. The information in Subheadings 3 and 4

detail both preclinical and clinical studies consistent with the hypothesis that MDD is associated with a hypodominergia is mesocorticolimbic structures.

3. ALTERED RESPONSES TO DOPAMINE AGONISTS FOLLOWING CHRONIC ANTIDEPRESSANT TREATMENTS

A fundamental inconsistency in biogenic-amine-based theories of depression is the lack of a temporal relationship between increases in synaptic concentrations of biogenic amines and an antidepressant action. Thus, in most double-blind, placebo-controlled studies, several weeks (usually ≥3) of antidepressant treatment are required to produce clinically meaningful improvement in depressive symptomatology. In contrast, changes in biogenic amine disposition are readily demonstrable both in vitro and following acute treatment. This so-called "therapeutic lag" is generally viewed as a period of antidepressant-induced molecular and cellular adaptation(s) that must precede symptom relief. The pioneering work of Vetulani and Sulser *(30)* marked the beginning of studies aimed at understanding the molecular bases for the adaptive process(es) responsible for this lag. During the past decade, several of the cellular adaptations produced by chronic antidepressant treatments have been shown to extend well beyond the aminergic synapse (reviewed in refs. *8, 31,* and *32*). Nonetheless, in preclinical studies, sensitization of mesolimbic dopamine receptors is perhaps the most consistent change produced by chronic antidepressant treatments. This sensitization is produced by structurally diverse antidepressants, as well as nonpharmacological interventions including electrocerebral silence (ECS) and rapid eye movement-sleep deprivation (reviewed in ref. *33*).

Serra et al. *(5)* first described changes in behavioral responses to the dopamine agonist, apomorphine, following chronic antidepressant treatments. These investigators observed a potentiation of the motor-stimulant effects of apomorphine, and a reduction in the hypomotility produced by lower doses of this drug. The motor stimulation produced by high doses of apomorphine has been attributed to stimulation of postsynaptic receptors, whereas its inhibitory effects have been linked to stimulation of dopamine autoreceptors that would inhibit dopamine release (reviewed in ref. *33*). The robust nature of the former phenomenon is supported by the demonstration that enhancement of motor activity following chronic (but not acute) antidepressant treatments is observed not only with apomorphine, but also with other, subtype selective dopamine agonists (e.g., quinpirole, 7-OHDPAT) *(34–36),* as well as amphetamine *(37)*. Further, these effects have been observed following chronic treatment with many agents (e.g., fluoxetine, imipramine, desimipramine, citalopram, mianserin, oxaprotiline, mirtazepine). In contrast, chronic antidepressant treatment does not appear to enhance the stereotypy produced by either direct (e.g., apomorphine, quinpirole) or indirect (e.g., amphetamine) acting dopaminergics *(34,37)*. These observations, when taken together with the ability of chronic antidepressants to enhance the motor stimulant properties of quinpirole and amphetamine injected directly to the nucleus accumbens *(38,39)*, indicate a selective perturbation of mesolimbic dopaminergic neurons. Because mesolimbic dopaminergic neurons play a key role in the control of motivation and reward-related behaviors that appear dampened in MDD (reviewed in ref. *40*), it can be hypothesized that the several weeks of antidepressant treatment required to produce this increased sensitivity to dopaminergic stimulation may contribute to the therapeutic lag common to biogenic-based antidepressants.

Despite the robust nature of this phenomenology, there have been several laboratories (e.g., ref. *41*) unable to demonstrate an increase in the motor-stimulant properties of dopaminergic agonists following chronic antidepressant treatments. These latter findings may be related to the mechanism(s) by which chronic antidepressants increase the behavioral sensitivity to dopamine agonists. Taken together with the multiple variables[1] in these studies and the tendency of laboratories not to strictly replicate, but rather modify and embellish, the number of reports confirming the ability of chronic antidepressant treatments to alter the behavioral responses to dopaminergic stimulation is remarkable. There is also evidence for a pharmacodynamic interaction between the antidepressant used for chronic treatment and the dopaminergic compound employed as the challenge. For example, in a study examining the locomotor responses of several dopamine agonists following chronic mirtazepine treatment, Rogoz et al. *(42)* reported the locomotor effects of amphetamine, but not quinpirole or 7-OHDPAT, were potentiated. This is perhaps expected in view of the potential number of intracellular targets affected by antidepressants *(31,43,44)*.

It has been more difficult to reproduce the initial observation made by Serra et al. *(5)* that chronic antidepressants prevent the hypomotility evoked by low doses of dopamine agonists. In some reports, this phenomenon was not observed in the presence of an increased locomotor response to higher doses of these same agents (e.g., refs. *34* and *37*). However, there have been behavioral studies confirming this phenomenon (e.g., ref. *45*; discussed in ref. *33*), as well as electrophysiological data *(46)* consistent with these findings. Nonetheless, the difficulty in reproducing this finding should not be viewed as suprising given the relatively narrow dose range for many of these drugs to produce a hypomotility (and the difficulties inherent in measuring a "floor" effect), the number of dependent variables in designing such a study, and the possibility that specific antidepressants perturb a subset of potential targets.

Behavioral studies with selective dopamine receptor agonists like quinpirole and 7-OHDPAT indicate that, at minimum, chronic treatment with most antidepressants alter the responsiveness of D2/D3 receptors, and that these antidepressant-induced changes appear largely confined to the mesocorticolimbic system. Studies using *in situ* hybridization and receptor autoradiography are consistent with the hypothesis that chronic antidepressants can increase the expression of mRNA encoding D2 and/or D3 receptors and radioligand binding to these receptors. Whereas early studies using [^{3}H]raclopride and other antagonists failed to demonstrate antidepressant-induced changes in radioligand binding to dopamine receptors (reviewed in ref. *33*), Rogoz and Dziedzicka-Wasylewska *(47)* reported chronic treatment with imipramine, citalopram, and mianserin increased [^{3}H]quinpirole but not [^{3}H]raclopride binding to both caudate nucleus and nucleus accumbens. Although these findings indicate that [^{3}H]agonists but not antagonists are capable of detecting antidepressant-induced changes in dopamine receptors, in a subsequent study using different antidepressants (tianeptine and fluoxetine), this group reported increases in both [^{3}H]quinpirole and raclopride binding to the caudate nucleus and the core of the nucleus accumbens *(48)*. Ainsworth et al. *(49)*

[1]Consider some of the variables in such a study: antidepressant, dose and dosing regimens, rat strain, challenge dose(s) of dopamine agonists, agonist employed (and dopamine receptor selectivity of this agent), and method of measuring behavior.

reported that chronic (14-d) treatment with fluoxetine and desipramine increased "D2-like" binding (i.e., binding to $D_{2,3, \text{ and/or } 4}$ receptors) to the shell of the nucleus accumbens, whereas a higher dose of fluoxetine also increased ligand binding to the core of the nucleus accumbens. The monoamineoxidase (MAO) inhibitor tranylcypromine did not affect radioligand binding to the nucleus accumbens, but reduced ligand binding to the ventromedial and dorsolateral striatum. In the same study, Ainsworth et al. *(49)* measured levels of mRNA, encoding D1 and D2 receptors. None of the antidepressants affected expression of D1 mRNA whrereas all three compounds increased D2 mRNA expression in the shell of the nucleus accumbens. The ability of tranylcypromine to increase D2 mRNA but not ligand binding may reflect the difference in specificity between the radioligand (that binds to D2, D3, and D4 receptors), and the mRNA probe. Alternatively, temporal differences between changes in the expression of mRNA and receptor protein could account for this apparent discrepancy following tranylcypromine.

Lammers et al. *(50)* examined the expression of mRNA encoding D3 receptors following administration of several antidepressants for up to 42 d. With the exception of fluoxetine, by 21 d each of the antidepressants (at a single-dose level) increased the expression of D3 mRNA, but apparently in a region-selective fashion. All of the compounds (desipramine, imipramine, amitryptiline, tranylcypromine) except fluoxetine increased expression in the nucleus accumbens shell, whereas desipramine increased expression in frontal cortex, septum, olfactory tubercle, and the Islands of Callejo. Similar, drug × region interactions were observed following 21 d of treatment with the other antidepressants. It is noteworthy that fluoxetine decreased D3 mRNA expression in nucleus accumbens, which can be contrasted with its effect on expression of D2 receptors *(49)*. Further, when drug-induced effects on D3 mRNA expression are compared over time, different temporal patterns emerge among the brain regions examined. If radioligand binding to D3 receptors was used as the dependent variable, a different drug × duration of treatment × region interaction emerges *(50)*. Of note is the observation in the Lammers et al. *(50)* study that ligand binding in the control group appeared to decrease in a time-dependent fashion; by 42 d of saline injection, ligand binding to D3 receptors in accumbens was significantly lower compared to values at 10 d. Fluoxetine-induced reductions in D3 mRNA expression at 21 d had returned to control values by 42 d of treatment, whereas ligand binding to the shell of the accumbens actually increased at this time point compared to controls. The Lammers et al. *(50)* study amply illustrates how a snapshot (i.e., examination of a drug-induced change at one time point [or dose, or brain region]) may not adequately portray either the effect(s) of a particular drug or model the clinical situation.

A number of other studies (e.g., refs. *18, 36, 48, 51,* and *52*) have also reported that chronic antidepressants increase either radioligand binding and/or expression of mRNA encoding D2/D3 receptors in mesolimbic structures. Most of these studies used a fixed treatment duration or dose of drug; several of these studies merit special comment. For example, Dziedzicka-Wasylewska et al. *(18)* reported that chronic (5-wk) treatment with imipramine and fluoxetine increased the expression of mRNA encoding D2 (but not D1 receptors) in the shell of the nucleus accumbens. No effects on D2 (or D1) mRNA expression were observed in the core of the nucleus accumbens. Increases in D2 mRNA expression were also present in the lateral but not medial portions of the caudate

putamen. In these studies, imipramine but not fluoxetine significantly elevated D2 mRNA expression in the medial and lateral ventral tegmenal area. Both regimens were sufficient to restore sucrose intake in a parallel group of animals subjected to CMS and, as discussed earlier, this regimen of CMS (sufficient to produce significant reductions in sucrose consumption) significantly reduced in D2 mRNA in the shell of the nucleus accumbens—an effect partially restored by both imipramine and fluoxetine.

Rogoz et al. *(42)* reported chronic treatment with mirtazepine potentiated the locomotor stimulant effects of amphetamine whereas the stimulant effects of both 7-OHDPAT and quinpirole were unchanged. No changes in either radioligand-binding to dopamine receptors or mRNA expression were observed in mesolimbic areas. Mirtazepine affects multiple aminergic systems (it has indirect 5-HT_{1A} receptor-stimulating properties and appears to function as an $\alpha 2$ and 5-HT_2 receptor antagonist), but is not a classical reuptake blocker. Berendsen et al. *(53)* have shown that acute treatment of mirtazepine modulates the behavioral effects of haloperidol, inhibiting its cataleptic action and enhancing its ability to inhibit apomorphine-induced climbing. This latter report indicates the ability of mirtazepine to affect dopamine receptor function following acute administration may preclude the long-term changes in postsynaptic dopamine receptors observed after other, biogenic-amine-based antidepressants. Nonetheless, the increased sensitivity to amphetamine (but not to either quinpirole or 7-OHDPAT) produced by chronic mirtazepine administration indicates this antidepressant does enhance dopaminergic tone, albeit in a manner different than reuptake inhibitors.

In toto, this body of preclinical evidence indicates chronic antidepressant treatments do enhance dopaminergic "tone" in mesocorticolimbic pathways. Given the potential number of downstream targets impacted by biogenic-amine-based antidepressants *(8,31,43)*, it is perhaps not surprising that these agents produce multiple changes in dopaminergic pathways in an apparent drug-, dose-, region-, and time-dependent fashion. The few clinical studies in this area do not provide definitive corroborative evidence of antidepressant-induced changes in dopamine receptors. Ebert et al. *(54)* reported no changes in the binding of the single-photon emission computed tomography (SPECT) ligand IBZM to striatal dopamine receptors between nondepressed and depressed individuals. Further, antidepressant treatment did not alter IBZM-binding in the depressed cohort as a whole. However, if the depressed group were divided into responders and nonresponders, antidepressant therapy reduced ligand binding in the (five) improved patients. The authors interpret this reduction as the result of an antidepressant-induced increase in the tonic release of dopamine, an interpretation compatible with data from preclinical studies (e.g., refs. *49* and *55*). Using radioligand binding to measure D1 and D2 receptors, Bowden et al. *(56)* reported no differences in receptor densities in postmortem samples of the caudate, putamen, and nucleus accumbens of suicide victims with a diagnosis of depression (and had been antidepressant-free for at least 3 mo) compared to matched controls. Increased densities of D2 receptors were noted in all of these brain regions from the suicide victims who had been treated with antidepressants. Although these investigators argue that the increased density of D2 receptors could be attributed to concurrent treatment with neuroleptics, these findings are also compatible with many of the preclinical studies described in this section. A more recent study examining D2 receptors in the caudate nucleus of depressed suicide victims *(57)* found no evidence for changes in the B_{max} of [^{3}H]raclopride, but did report a significant reduction in affinity of

this radioligand in a subgroup of individuals. Clearly, additional clinical studies are needed to determine if antidepressant-induced changes in dopaminergic pathways documented in preclinical studies are relevant to the human condition.

4. PHARMACOLOGY OF DOPAMINERGIC DRUGS IN MDD

Clinical studies indicate that an increase in dopaminergic "tone," produced either by blockade of dopamine transporters or via direct stimulation of postsynaptic dopamine receptors, is sufficient to produce an antidepressant action. For example, bupropion (Wellbutrin®) is a dopamine reuptake inhibitor *(26,58)* that is as effective as SSRIs in the treatment of MDD (reviewed in ref. *59*). However, bupropion is not a high-affinity inhibitor of dopamine reuptake *(26)*, nor is it selective for the dopamine transporter. Bupropion has been reported to act as a nicotinic antagonist *(60)*, and inhibits norepinephrine reuptake *(26,58)*. Because selective inhibition of norepinephrine reuptake is sufficient to produce an antidepressant action (reviewed in ref. *61*), this latter action could either contribute to or explain the antidepressant effects of bupropion. In preclinical studies, the potency of bupropion to inhibit firing of noradrenergic neurons in locus coeruleus (13 mg/kg, ip, rats) approximates its ED_{50} in the forced swim test (10 mg/kg) *(58)*. The forced swim test, although lacking the face and construct validity of a true model of depression, is an excellent predictor of clinically effective antidepressants *(62,63)*. Further, in the Cooper et al. *(58)* study, inhibition of midbrain dopaminergic neurons was observed only at fourfold higher doses of bupropion. At face value, the nicotinic antagonist properties of bupropion (which may well contribute to its use in smoking cessation) would not contribute to its antidepressant properties. Thus, nicotine appears to mimic the actions of antidepressants in both preclinical (e.g., ref. *64*) and clinical *(65)* studies.

Perhaps more compelling evidence that activation of dopaminergic pathways can produce an antidepressant action is derived from clinical studies demonstrating that direct-acting dopamine agonists are antidepressant. There have been several double-blind trials comparing the dopamine (D2/D3 receptor-preferring) agonist bromocriptine to tricyclic antidepressants (imipramine and amitriptyline) in depressed patients. Although these trials *(66–68)* are small by contemporary standards, in each instance, bromocriptine appeared as effective as a tricyclic in reducing Hamilton Depression rating scale scores. Nausea was the most prominent side effect in these studies. There have been a number of open trials using bromocriptine (reviewed in ref. *69*) with small numbers of patients; most of these trials report an antidepressant response to bromocriptine. At face value, these data support the hypothesis that dopamine receptor activation is sufficient to effect an antidepressant action, thereby implicating dopamine receptors in depression. It should be noted that the PDSP database (http://.crwu.edu/pdsp.asp) indicates that bromocriptine also binds with nM affinities to a number of serotonin receptor subtypes (e.g., 5HT1A, 6, and 7) that may contribute to its therapeutic effects.

The antidepressant properties of the D3 receptor-preferring agonist pramipexole have also been examined in a double-blind, placebo-controlled trial. In this study, three doses of pramipexole were compared with a standard dose of fluoxetine and placebo. By end point (8 wk), patients receiving an intermediate dose of pramipexole (1 mg/kg) significantly improved compared to placebo in the three depression rating scales employed Hamilton Rating Scale for Depression (HAM-D), Montgomery–Asberg Depression Rating Scale (MADRS), and Clinician's Global Impressions-Severity of Illness (CGI-SI). The

most dramatic improvement was manifested in the high-dose pramipexole group (5 mg/kg), although the dropout rate at this dose precluded statistical comparisons *(70)*. Pramipexole has also been shown to significantly reduce MADRS scores and a patient self-rating scale in an open-label study of Parkinson's patients receiving levodopa-(L-dopa) *(71)*. The daily dose of L-dopa was significantly reduced during this period, which may have contributed to the improvement in mood. Nonetheless, these data are consistent with the report of Corrigan et al. *(70)* that pramipexole has antidepressant properties.

When used in a combination strategy with "traditional" antidepressants *(72)*, dopaminergic agents have been reported to improve depressed mood in patients, including those patients either resistant to, or exhibiting only a partial response to serotonin and/or norepinephrine reuptake inhibitors. Several studies have reported that addition of bupropion, most often to SSRIs such as paroxetine and fluoxetine resulted in greater symptomatic improvement than when either drug was used alone *(73–75)*. The ability of bupropion to inhibit norepinephrine reuptake does not permit an unequivocal assignment of this effect to its inhibition of dopamine reuptake. However, in one study *(75)*, bupropion-enhanced responses combined with venlafaxine, a dual-uptake inhibitor. Nonetheless, bupriopion inhibited the *O*-demethylation of venlafaxine, which further confounds interpretation of this study.

Perhaps more compelling evidence that dopaminergic receptor activation augments the effects of traditional antidepressants derives from studies using dopamine agonists. One preclinical study is of particular interest in this context. Maj and coworkers *(76)* demonstrated that pramipexole had a synergistic action in the forced swim test when combined with dual-uptake inhibitors (amitryptiline, imipramine). Further, SSRIs (which are generally reported as inactive in the rat variant of this procedure) such as fluoxetine potentiate the antidepressant-like actions of pramipexole in the forced swim test *(76)*. In the more realistic CMS model, dopamine agonists (quinpirole and bromocriptine and pramipexole), like other antidepressants *(15)*, restored stress-induced deficits in sucrose consumption.

In open trials, Koyama and coworkers *(77,78)* used bromocriptine and pergolide in patients resistant to (but concurrently maintained on) traditional antidepressants. In both studies, clinical improvement was noted in a significant proportion of patients following addition of a dopamine agonist. Lattanzi et al. *(79)* examined the effects of adding pramipexole to traditional antidepressants in patients classified as drug-resistant. In this 4 mo study using inpatients (both unipolar and bipolar depression), highly significant reductions in MADRS and clinical global impression were obtained, with 67.7% considered responders on MADRS, and 74.2% on CGI, respectively. Perugi et al. *(80)* examined the effects of pramipexole or ropinirole in treatment-resistant bipolar disorder. In this open study, dopamine agonists were added to conventional antidepressants and mood stabilizers; for inclusion in this study patients had not responded to this combination of drugs for at least 8 wk. Eight patients (44.4%) were considered responders (four pramipexole and four ropinerole, respectively) with five patients exhibiting a marked improvement (CGI = 1), and three moderate improvement (CGI = 2), respectively. Based on retrospective chart review, Sporn et al. *(81)* reported that adjunctive use of pramipexole improved 40% and 50% respectively of patients with unipolar and bipolar depression based on marked to moderate improvement in the CGI-I (improvement) scale. *In toto*, this body of clinical literature indicates that increasing dopaminergic tone improves response to conventional antidepressants in a refractory subpopulation of patients with

both unipolar and bipolar depression. However, the clinical studies described here are generally quite small (<20 patients) and have an open design. In the ideal, double-blind, controlled studies (that are appropriately powered) will be required to rigorously test the hypothesis that increasing dopaminergic tone augments the effect of conventional agents.

5. THE "BROAD SPECTRUM" ANTIDEPRESSANT: COMBINING DOPAMINE, NOREPINEPHRINE, AND SEROTONIN REUPTAKE BLOCKADE IN A SINGLE MOLECULE

The efficacy of the prototypic tricyclic, imipramine, had a profound influence on the development of pharmacotherapies for MDD. Follow-on agents (e.g., desmethylimipramine, nortryptyline, amitryptyline), produced by modification of the tricyclic structure, constitute a family of dual-uptake inhibitors, albeit with different relative potencies at serotonin and norepinephrine transporters *(26,82)*. Selective reuptake inhibitors (e.g., SSRIs, such as fluoxetine, paroxetine, and citalopram) have, in large part, supplanted tricyclic antidepressants as the standard of care because, as a group, SSRIs are safer and easier to use. Nonetheless, there is evidence, although not unequivocal, that dual-uptake inhibitors are more effective than SSRIs, particularly in the treatment of severely depressed individuals. A "second generation" of dual-reuptake inhibitors (e.g., venlafaxine and duloxetine) with a "cleaner" side-effect profile than tricyclics may well replace SSRIs as the drugs of choice for MDD.

These newer compounds, although safer and easier to use than the tricyclics, do not offer clearly demonstrable advantages with respect to either speed of onset or efficacy.[2] Given the preclinical and clinical findings described in the previous sections, drug development strategies directed at simultaneously increasing synaptic concentrations of dopamine, norepinephrine, and serotonin could result in a more rapid onset of relief and/or greater efficacy than single-or dual-uptake inhibitors. In theory, there are a number of strategies that may be employed to accomplish this goal *(83)*. Among biogenic-amine-based approaches, a compound capable of inhibiting the reuptake of norepinephrine, serotonin, and dopamine is perhaps the most straightforward. Such compounds have been termed "broad spectrum antidepressants" *(83)*. Because the dopamine, serotonin, and norepinephrine transporters belong to a gene family of 12 transmembrane transporters *(84)*, the design and synthesis of a triple-reuptake inhibitor appears, at face value, straightforward. However, the design of *bioavailable*, *safe*, and *well-tolerated* molecules active at all three transport proteins represents a formidable synthetic challenge.

Substituted azabicyclo[3.1.0]hexanes (exemplified by sibling molecules DOV 21,947 and DOV 216,303) have been identified as orally available, triple-reuptake inhibitors *(85,86)*. Phase I studies with the more advanced compound, DOV 216,303 (manuscript in preparation), have demonstrated that this compound is safe and well tolerated. This compound is currently in a Phase II trial for the treatment of MDD. In HEK 293 cells expressing a recombinant form of the corresponding human transporter protein, DOV 216,303 inhibits [^{3}H]norepinephrine and [^{3}H]serotonin uptake with equal potency, and is approximately four-fold less potent as an inhibitor of [^{3}H]dopamine uptake (Table 1) *(85)*.

[2]The term *efficacy* in this context can reflect a variety of outcome measures, such as an increase in the percentage of patients with a significant reduction in depressive symptomatology, an increase in the percentage of patients achieving remission, and/or a decrease in the percentage of individuals relapsing.

Table 1
DOV 216,303 Inhibits [^{3}H] Biogenic Amine Uptake

	[^{3}H]5-HT	[^{3}H]DA	[^{3}H]NE
DOV 216,303	13.8 ± 1.5	78 ± 15	20.3 ± 6.1
Fluoxetine	7.3 ± 2.9	10^5	1020 ± 18
Imipramine	8.0 ± 2.3	$>10^5$	70 ± 21
Desmethylimipramine	64 ± 17	$>10^5$	4.2 ± 1.1

Human recombinant neurotransmitter transporters were expressed in HEK-293 cells exactly as described in Eshleman *(26)*. [^{3}H]Serotonin (5-HT), dopamine (DA), and norepinephrine (NE) were used to measure reuptake at the human serotonin, dopamine, and norepinephrine transporter, respectively exactly as described in Eshleman *(26)*. Values (IC_{50}, nM) represent the X ± SEM of at least three independent experiments for DOV 216,303 *(85)*. Values for the other antidepressants are shown for comparison; these data are from Eshleman *(26)*.

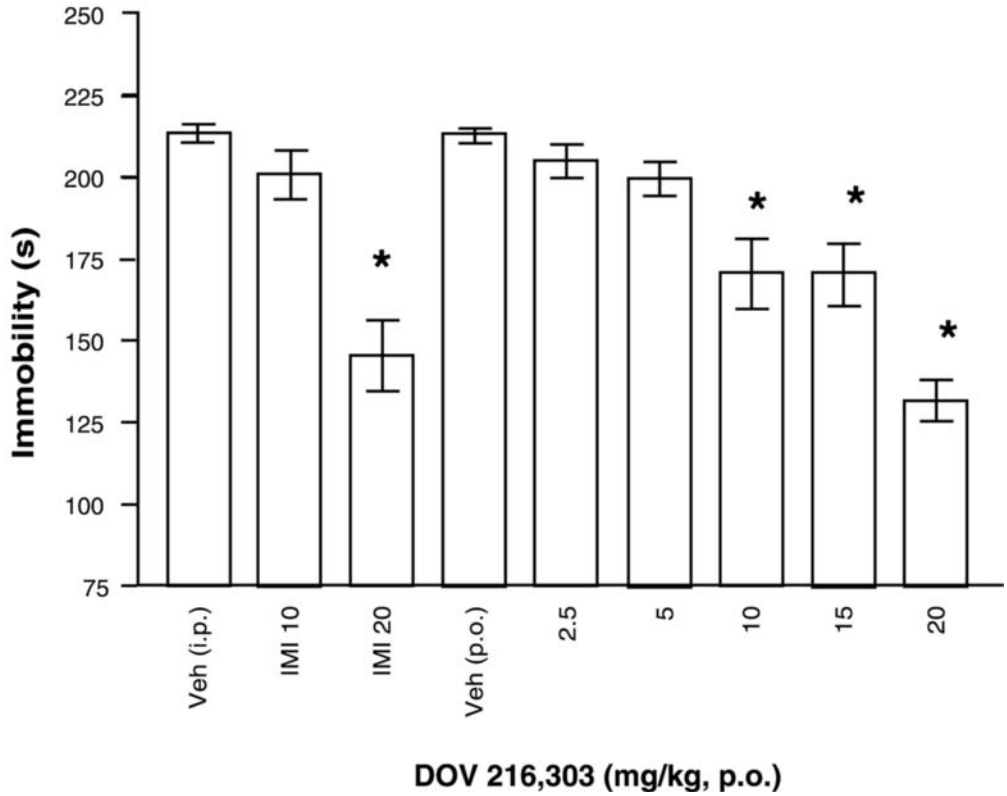

Fig. 1. Effect of DOV 216,303 in the forced swim test. Imipramine (intraperitoneal), DOV 216,303 (oral), or vehicle were administered to male, Swiss albino mice 60 min prior to testing. The duration of immobility was measured for the last 4 min of a 6-min test as described *(89)*. Values represent X ± standard error of mean of ≥6 mice/group. Symbol: *, $p < 0.001$, Dunnett's multiple comparison test. These data are from Skolnick *(85)*.

The optimum potency ratios for inhibiting uptake at the three transporters are unknown. However, among currently used "single" and "dual" reuptake inhibitors, the potency ratios (serotonin IC_{50}:norepinephrine IC_{50}) span several orders of magnitude, ranging from citalopram at one extreme (~3000-fold more selective as an inhibitor of serotonin

reuptake) to milnacipran, which is about equipotent as an inhibitor of norepinephrine and serotonin reuptake *(61,82)*. Nonetheless, based on in vitro potencies in recombinant human receptors expressed in HEK 293 cells (Table 1), the plasma levels of DOV 216,303 attained in Phase I studies would be sufficient to significantly inhibit uptake of all three biogenic amines (ref. *86* and manuscript in preparation). Further, based on the potency of azabicyclo[3.1.0]hexanes in behavioral despair models *(85,86)* these compounds must readily cross the blood–brain barrier.

DOV 216,303 and DOV 21,947 are orally active and potent *(85,86)* in behavioral despair models such as the forced swim *(87)* and tail suspension *(88)* tests (Fig. 1). Like clinically active antidepressants, these compounds reduce immobility in both procedures at doses that do not stimulate motor activity *(85)*. These behavioral despair procedures, although highly predictive of antidepressant activity in humans *(62,63)*, do not yield useful information about either onset of action or efficacy. Although preclinical and clinical data indicate that such a broad-spectrum antidepressant will be superior to serotonin and/or norepinephrine reuptake inhibitors, the ultimate test of this hypothesis will be in the clinic.

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