REVIEW

The Role of Dopamine in the Pathophysiology of Depression

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Multiple sources of evidence support a role for diminished dopaminergic neurotransmission in major depression. The physiological alterations underlying reduced dopamine (DA) signaling could result from either diminished DA release from presynaptic neurons or impaired signal transduction, either due to changes in receptor number or function and/or altered intracellular signal processing. There are data supporting each of these mechanisms, although interpretation of previous research is confounded by issues around study population, medication status, and technological limitations. In some patients with depression, DA-related disturbances improve by treatment with antidepressants, presumably by acting on serotonergic or noradrenergic circuits, which then affect DA function. However, most antidepressant treatments do not directly enhance DA neurotransmission, which may contribute to residual symptoms, including impaired motivation, concentration, and pleasure. Animal models of major depression show considerable responsiveness to manipulations of DA neurotransmission. Several studies, including postmortem investigations, particularly of subjects with severe depression, have demonstrated reduced concentrations of DA metabolites both in the cerebrospinal fluid and in brain regions that mediate mood and motivation. Although the neuroimaging findings are not unequivocal, several studies support the hypothesis that major depression is associated with a state of reduced DA transmission, possibly reflected by a compensatory up-regulation of D_2 receptors. These alterations in DA signaling may underlie the findings of increased "liking" or "high" feelings reported by severely depressed subjects treated with d-amphetamine compared with the response of less severely ill and normal control subjects. The efficacy of medications that directly act on DA neurons or receptors, such as monoamine oxidase inhibitors and pramipexole, suggests that subtypes of depression stemming from a primary DA dysfunction exist. Further research on the contribution of DA to the pathophysiology of depression is justified to improve outcomes for patients with treatment-resistant and nonremitting depression.

Motivation, psychomotor speed, concentration, and the ability to experience pleasure are all linked in that (1) they are regulated in part by dopamine (DA)–containing circuits in the central nervous system and (2) impairment of these functions are prominent features of depression. Despite this theoretical underpinning, research on the role of DA in depression has been largely overshadowed by research on norepinephrine (NE)- and serotonin (5HT)-containing circuits. Recent findings clearly warrant scrutiny of the role of DA in the pathophysiology of depression and, moreover, whether there exists a "dopaminergic dysfunction" subtype, characterized by a poor response to antidepressants that act primarily on 5HT or NE neurons. There is now an emerging consensus that the majority of depressed patients treated with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) do not attain remission.[1] It is our contention that this is due, in part, to the lack of effects of SSRIs and SNRIs on DA neurons.

The original monoamine hypothesis of depression emerged largely from the ob-

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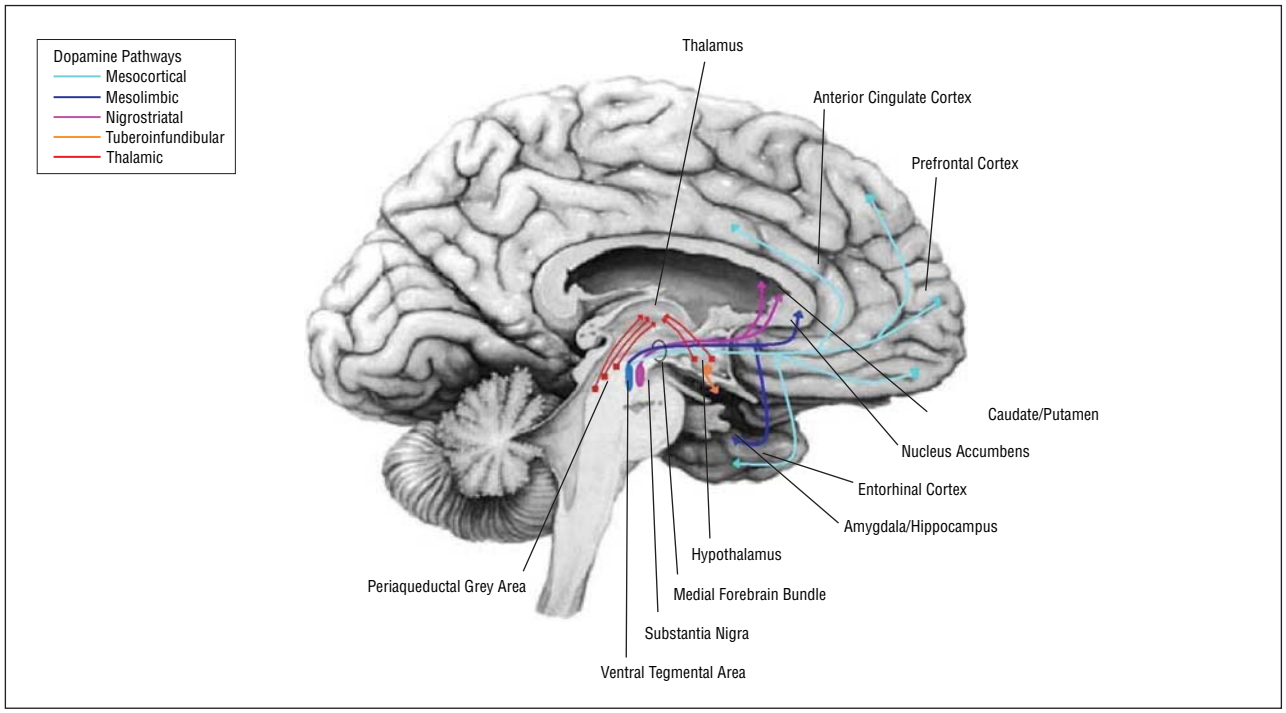

Figure 1. Dopaminergic pathways in the human brain. Reprinted with permission from Szabo et al (2004)[5] and Sanchez-Gonzalez et al (2005).[6] (Brain drawing used with the permission of Robert Finkbeiner.) Note that this image is a midline sagittal section of the brain. Many of the structures identified are located more laterally than the drawing indicates.

served effects on mood of reserpine, which depletes vesicular monoamine stores and reduces mood; of amphetamine, which briefly increases synaptic concentrations of monoamines, and raises mood; and of monoamine oxidase inhibitors (MAOIs), which increase the central nervous system concentrations of monoamines and are, of course, effective antidepressants.[2,3] Although these agents all affect DA similarly to NE and 5HT, it wasn't until the mid 1970s that a role for DA in depression was postulated.[4] The primary reason for the limited focus on DA was the finding that the efficacy of tricyclic antidepressants (TCAs) stemmed from their ability to inhibit the reuptake of NE and/or 5HT. However, a long-standing conundrum associated with the original monoamine hypothesis is that the reuptake inhibiting effects of TCAs (and SSRIs and SNRIs) occur within hours of drug ingestion, but their antidepressant effects take longer to occur. This temporal discrepancy implies that other mechanisms must be involved in recovery from a depressive episode.

There is now a convergence of data from animal models, genetics, neuroimaging, and human clinical trials that strengthen the case for DA dysfunction in the pathophysiology of major depression, at least in a significant subgroup of patients. This monograph comprehensively reviews the current evidence with subsequent recommendations for future studies of dopaminergic signaling in depression and its treatment.

DOPAMINERGIC PATHWAYS IN THE CENTRAL NERVOUS SYSTEM

Most DA-producing neurons in the brain are located in brainstem nuclei: the retro-rubro field (A8), substantia nigra pars compacta (A9), and the ventral tegmental area (VTA) (A10). Projection pathways of the axons arising from these cell bodies follow 1 of 3 specific paths (with some overlap) via the medial forebrain bundle to innervate specific cortical and subcortical structures, unlike the more diffuse innervation patterns of serotonergic and noradrenergic cells (**Figure 1**). The nigrostriatal pathway projects from the substantia nigra pars compacta to the dorsal striatum (caudate and putamen) and has a prominent role in the motor planning and execution of movement, although it clearly also plays an important role in nonmotor functions, such as cognition.[7] The mesocortical pathway arises from the VTA and projects to the frontal and temporal cortices, particularly the anterior cingulate, entorhinal, and prefrontal cortices. This pathway is believed to be important for concentration and executive functions such as working memory. The mesolimbic pathway also arises in the VTA but projects to the ventral striatum (including the nucleus accumbens), bed nucleus of the stria terminalis, hippocampus, amygdala, and septum. It is particularly important for motivation, the experience of pleasure, and reward.

Aspects of anterior pituitary function are also under dopaminergic control. The tuberoinfundibular pathway arises from the arcuate nucleus of the hypothalamus (A12) and projects to the median eminence of the hypothalamus, where DA released into the portal vessels acts to inhibit the secretion of prolactin from the anterior pituitary.[8] This pathway is also involved in dopaminergic regulation of growth hormone release from the anterior pituitary.[9] The incertohypothalamic pathway originates from cell bodies in the medial portion of the zona incerta (A13) and innervates amygdaloid and hypothalamic nuclei involved in sexual behavior.

Recently, significant dopaminergic innervation of the thalamus has been demonstrated in primates, although it is largely absent in rodents.[6] Unlike the other dopaminergic pathways, this "thalamic dopamine system" arises from multiple sites, including the periaqueductal gray matter, the ventral mesencephalon, hypothalamic nuclei, and the lateral parabrachial nucleus. This DA pathway may contribute to the gating of information transferred through the thalamus to the neocortex, striatum, and amygdala.

DOPAMINE SYNTHESIS AND SIGNALING

Dopamine is synthesized in the cytoplasm of presynaptic neurons from the amino acids phenylalanine and tyrosine (**Figure 2**). Dopamine exerts its effects on the postsynaptic neuron through its interaction with 1 of 5 subtypes of dopamine receptors, divided into 2 groups, the dopamine 1 (D_1) family (comprising the D_1 and D_5 subtypes) and the D2 family (comprising the D_2, D_3, and D_4 subtypes) (**Table 1**). The structure of all of the receptor subtypes conforms to the structural model for a G-protein coupled receptor with 7 membrane-spanning alpha-helices and an extracellular amino terminal. Each receptor subtype has a characteristic anatomical distribution with the D_1 and D_2 subtypes present in significantly greater amounts than the others.[12]

On binding an agonist, D_1 and D_5 receptors activate the adenylate cyclase second messenger system, elevating intracellular cyclic adenosine monophosphate concentrations. Cyclic adenosine monophosphate increases protein kinase A activity with resulting changes in activity levels of enzymes or other proteins within the cell. D_1 receptors may also activate other second messenger pathways, perhaps contributing to intracellular cross-talk between D_1 and D_2 receptors.[13] The D_2 family of receptors, when stimulated, all reduce adenylate cyclase activity. Somatodendritic and presynaptic D_2 receptors also function as autoreceptors with activation of somatodendritic D_2 receptors resulting in reduced DA cell firing and activation of presynaptic D_2 receptors reducing the amount of DA released per action potential.[5]

In the basal ganglia, DA is cleared from the extracellular space primarily by presynaptic nerve terminal uptake mediated by the dopamine transporter (DAT). The prefrontal cortex in man and nonhuman primates represents something of an anomaly in that there is an absence of DAT on DA nerve terminals.[14] Consequently, the DA signal is terminated by DA uptake into NE terminals by the norepinephrine transporter (NET) (**Figure 3**). Postsynaptically, DA is inactivated by catechol-o-methyl transferase (COMT). Both the A and B forms of monoamine oxidase (MAO-A and MAO-B) can metabolize DA, which, along with COMT, serially catabolizes DA to produce the intermediate breakdown products dihydrophenylacetic acid and 3-methoxytyramine before forming the final excretion product, homovanillic acid (HVA).

Dopamine signaling occurs in 2 forms. Phasic DA release results from burst firing of VTA neurons and is thought to occur in response to behaviorally salient stimuli, such as those that may predict reward.[15,16] This

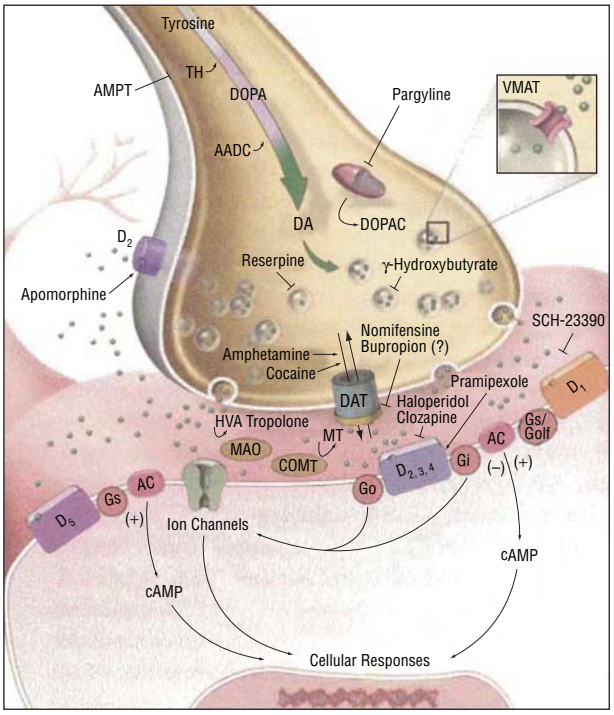

Figure 2. Dopaminergic synaptic signaling. Reprinted with permission from Szabo et al (2004).[5] AADC indicates aromatic acid decarboxylase; AMPT, α-methylparatyrosine; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; COMT, catechol-*O*-methyltransferase; D_1-D_5, dopamine receptors 1 through 5; DA, dopamine; DAT, dopamine transporter; DOPA, 3,4-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; Gi, Go, and Gs, protein subunits; HVA, homovanillic acid; MAO, monoamine oxidase; MT, 3-methoxytyramine; TH, tyrosine hydroxylase; and VMAT, vesicular monoamine transporter.

phasic DA release activates postsynaptic D_2 receptors and is terminated via reuptake by DAT. Tonic DA release arises from slow, irregular activity of the VTA, resulting in low concentrations of extracellular DA that act at presynaptic DA receptors to inhibit phasic DA neuron firing, and is subject to metabolism by COMT.[17]

There is considerable evidence that the DA system is dynamic, with up- and down-regulation of D_2 receptors and DAT based in part on DA availability. Reserpine, which depletes DA, induces a significant decrease in DAT density and reduces DA uptake. Similarly, amantadine, which in part acts to induce DA release, increases DAT density.[18] D_1 receptor density appears to be less responsive to changes in DA availability.

Although beyond the scope of this review, it should be noted that there is substantial evidence that DA signaling in the dorsal and ventral striatum serves in a gating capacity for glutamatergic inputs from the hippocampus, basolateral amygdala, thalamus, and prefrontal cortex.[19] Dopamine performs a similar gating function over the ability of the prefrontal cortex to regulate basolateral amygdala output.[20]

ANIMAL MODELS OF DOPAMINE FUNCTION IN DEPRESSION

Rodent models of depression demonstrate altered mesolimbic DA system function, and moreover, certain antidepressants act to enhance DA transmission.[21] Whether

Table 1. Characteristics of Dopamine Receptor Subtypes[10,11]

	D_1 Family		D_2 Family		
Characteristic	**D_1**	**D_5**	**D_2**	**D_3**	**D_4**
Homology with D_1	100	82	45	42	42
Homology with D_2	45	50	100	75	54
Second messenger effect	Increase AC	Increase AC	Decrease AC	Decrease AC	Decrease AC
Localization	Dorsal striatum Ventral striatum Thalamus Prefrontal cortex	Hippocampus Thalamus Striatum	Dorsal striatum Ventral striatum Pituitary	Ventral striatum Islands of Calleja	Frontal cortex Midbrain Amygdala Hippocampus Hypothalamus
Agonists*	SKF 38393 Pergolide Chloro-PB	Chloro-PB	Bromocriptine, pergolide, piribedil, pramipexole, quinpirole		PD 168077 Quinpirole
Antagonists	SCH 23390	SCH 23390	Sulpiride, typical antipsychotics raclopride		Clozapine PD 101387

Abbreviation: AC, adenylyl cyclase.
*Apomorphine is an agonist at all receptor subtypes.

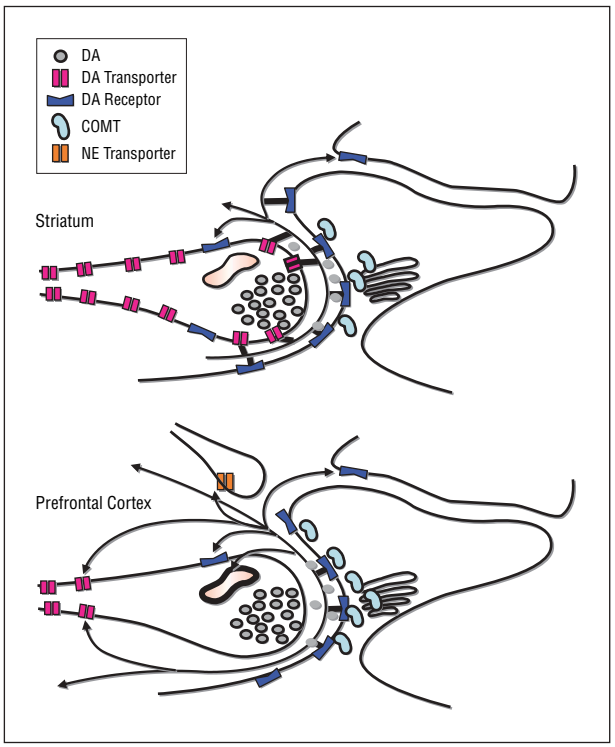

Figure 3. Differing structures of dopamine terminals in the striatum and prefrontal cortex. Reprinted with permission from Sesack et al (1998).[14] COMT indicates catechol-*O*-methyltransferase; DA, dopamine; and NE, norepinephrine.

these effects stem from induction of subsensitivity of DA autoreceptors or heightened responsivity of postsynaptic receptors, or both, is unclear, although the weight of the evidence most supports increased postsynaptic sensitivity, as first proposed by Spyraki and Fibiger.[22] This heightened sensitivity seems to be limited to the ventral striatum because the dose-response curve for DA-agonist–induced stereotypies (stemming from dorsal striatal DA receptor binding) is not shifted to the left by chronic antidepressant treatment. Evidence supporting this theory includes the findings that chronic treatment with electroconvulsive therapy, sleep deprivation, and virtually all antidepressants increases the motor stimulant effects of DA receptor agonists.[23] Chronic treatment with antidepressants (TCA, SSRI, or MAOI) for 21 days or 10 days of electroconvulsive treatments results in increased D_3 receptor messenger RNA (mRNA) expression in the nucleus accumbens.[24] A potential contributor to altered DA receptor sensitivity is prostate apoptosis response (Par-4) protein, a leucine zipper containing protein that regulates the activity of the D_2 receptor in neurons. Mutant mice lacking the component of Par-4 that interacts with the D_2 receptor demonstrate depressive behaviors.[25]

Impaired DA release is also proposed to contribute to the pathophysiology of depression. In so-called "effort expenditure" rodent models of depression, reduced DA concentrations in the nucleus accumbens correlate with reduced efforts by rodents to work for specific rewards.[26,27] Additionally, administration of TCAs or fluoxetine raises DA concentrations in the nucleus accumbens.[28] Transcranial magnetic stimulation applied to the rat frontal cortex increases extracellular DA concentrations in the striatum,[29] an effect also observed in humans.[30,31]

The chronic mild stress model has been suggested to have the best face validity of any animal model of depression in that repeated mild stresses over time gradually induce a state of decreased responsiveness to rewards and reduced sexual and aggressive behaviors.[32] Rodents exposed to this model demonstrate decreased D_2/D_3 receptor binding in the nucleus accumbens, which is reversed by chronic antidepressant treatment (TCAs, SSRIs, or mianserin).[33] When these "recovered" rodents are exposed to D_2/D_3 antagonists, decreased reward responding re-emerges.[34,35] Rodents exposed to chronic mild stress also show reduced responsiveness to the stimulatory effects on locomotion and reward of the D_2/D_3 agonist quinpirole.[35]

Two other animal models, "learned helplessness" and the "forced swim test," both use a reduction in locomotor activity under stress as proxies for depression.[36] Animals experiencing learned helplessness exhibit DA depletion in the caudate nucleus and nucleus accumbens, which can be prevented by pretreatment with DA agonists.[37,38]

In the forced swim test, immobility in rodents is reversed by D_2/D_3 agonists, nomifensine (a DA/NE reuptake inhibitor), and TCAs, and the effect of antidepressants can be inhibited by D_2/D_3 antagonists.[39,40]

HUMAN GENETIC AND NEUROCHEMICAL STUDIES

The heritability of major depression is estimated to be between 31% and 42% and is likely higher for individuals with recurrent major depression.[41] Although major depression is almost certainly a polygenetic illness, certain genes may influence the subtype of depression expressed, and the presence of more than 1 vulnerability gene may significantly increase the likelihood of developing this disorder.[41]

Polymorphisms of the D_4 receptor, DAT, and COMT have functional significance, although in a study of Jewish patients with major depression, no difference in the allelic distributions of these polymorphisms was found.[42] The D4 receptor is the most polymorphic of the DA receptors, possessing a 48 base pair variable number tandem repeat polymorphism in exon 3 of the gene with alleles in humans encoding for 2 to 10 repeats.[43] A recent meta-analysis of 2071 subjects in 12 studies identified the 2-repeat allele as a vulnerability allele for depression.[44] Others have identified a possible association between the Bal I polymorphism of the D_3 receptor and unipolar and bipolar depression.[45,46] Consistent associations between D_2 receptor or DAT polymorphisms and major depression have not been identified. Mutations in the gene for dopamine β-hydroxylase, the enzyme that converts DA to NE, can lead to elevations in the DA/NE ratio, potentially increasing the risk for psychotic symptoms in depression.[47] Depressed patients homozygous for methionine at the $COMT^{158\ (val\text{-}met)}$ polymorphism exhibited a less robust response to mirtazapine in a 6-week study.[48]

Studies comparing measures of DA neurotransmission between depressed and control groups require careful age-matching because there is a functionally significant and progressive loss of DA activity with advancing age, largely due to a loss of DA neurons.[49] The majority of studies examining the concentration of DA metabolites in cerebrospinal fluid, primarily HVA, found lower concentrations in depressed patients compared with controls, particularly in patients with psychomotor retardation.[4,50-57] Some discrepant results have also appeared.[58,59] Low pretreatment cerebrospinal fluid HVA concentrations have failed to consistently predict response to TCA treatment,[60] although individual studies have found an inverse association between cerebrospinal fluid HVA concentrations and the magnitude of clinical response to levodopa,[56] piribedil,[61] and nomifensine.[62] Of note, however, is one study of 40 unipolar or bipolar depressed inpatients with psychomotor retardation in which the rank order of effectiveness of 3 antidepressants and placebo correlated with their prodopaminergic effects.[63]

In a unique study using internal jugular venous sampling, medication-free, treatment-resistant, unipolar depressed patients were found to exhibit reduced concentrations of both NE and its metabolites and HVA, but not 5-hydroxyindoleacetic acid, compared with healthy controls.[64] Estimates of brain DA turnover were inversely correlated with the severity of depressive illness as measured by the Hamilton Depression Scale. Others have reported that the lymphocytes of depressed patients have significantly lower D_4 receptor mRNA expression compared with controls, with normalization after 8 weeks of paroxetine treatment.[65] In contrast to these findings, psychotically depressed patients demonstrate elevated concentrations of plasma DA and HVA, lower serum dopamine β-hydroxylase activity, and increased cerebrospinal fluid concentrations of HVA.[66]

Apomorphine, a DA agonist, has been used as a probe to assess DA receptor responsiveness in depression. Acting on DA receptors in the arcuate nucleus of the hypothalamus, apomorphine stimulates the release of growth hormone–releasing hormone, which acts to increase peripheral growth hormone concentrations. The majority of studies have found no difference in growth hormone response to apomorphine between depressed and healthy control subjects.[67] However, a Belgian group has repeatedly reported a blunted growth hormone response to apomorphine administration in suicidal, but not nonsuicidal, depressed patients.[68,69] Similar mixed findings exist for the effect of apomorphine on peripheral prolactin concentrations.[67,70] The extent to which DA modulation of an endocrine response reflects DA functioning in the mesocortical, mesolimbic, and nigrostriatal pathways is unknown.

An additional impetus to seek DA involvement in depression is the unduly high frequency of depression among patients with Parkinson disease. The incidence of major depression in community samples of patients with Parkinson disease is 5% to 10% with an additional 10% to 30% experiencing subsyndromal depressive symptoms.[71] In addition, high frequency deep brain stimulation of the left substantia nigra led to dramatic and severe transient depression in 1 subject with Parkinson disease.[72]

DISTURBED REWARD SYSTEM FUNCTION IN DEPRESSION

Anhedonia, the absolute or relative inability to experience pleasure, is 1 of 2 symptoms required for the diagnosis of major depression. Of the putative endophenotypes of major depression, the anhedonic form is one of the most well supported.[73] Dopamine neurons have long been known to be critical to a wide variety of pleasurable experiences and reward. Severity of major depressive disorder has been found to correlate highly with the magnitude of reward experienced after oral d-amphetamine, which increases DA availability by a variety of mechanisms.[74] In particular, medication-free, severely depressed subjects experienced greater reward than controls while those with milder forms of depression did not differ from the control group. One explanation for these findings is that in severe depression, there is a reduction in DA release, resulting in compensatory mechanisms, such as up-regulation of postsynaptic DA receptors and decreased DAT density, which taken together would increase DA signal transduction resulting from amphetamine-induced DA release into the synapse. These findings have now been confirmed and extended in a recent study using functional magnetic resonance imaging to

assess the activity of brain reward systems after d-amphetamine challenge in 12 drug-free depressed patients and 12 matched controls. The depressed subjects had a markedly greater behavioral response to the rewarding effects of the psychostimulant and altered brain activation of the ventrolateral prefrontal cortex, orbitofrontal cortex, caudate, and putamen.[75] These findings further implicate DA circuit dysfunction in major depression.

The finding of increased reward with psychostimulant administration in severely depressed patients may possibly be related to the finding that glucocorticoids may selectively facilitate DA transmission in the nucleus accumbens.[76] In healthy control subjects, cortisol levels are positively associated with d-amphetamine–induced DA release in the ventral striatum and dorsal putamen. Subjects with higher plasma cortisol concentrations report greater positive drug effects.[77] This work is supported by the finding that, when exposed to a psychosocial stressor, ventral striatal DA concentrations are increased among subjects who report poor early life maternal care compared with those who do not, and the DA increase is correlated with the increase in salivary cortisol concentrations.[78] The high incidence of hypercortisolemia in depression, particularly in severe depression, raises speculation that elevated cortisol concentrations alter dopaminergic reward systems, thereby altering hedonic responsiveness. One proposed model posits that over time, frequent bouts of stress associated with intermittent increased exposure to glucocorticoids sensitizes the mesolimbic DA system.[77] In a test of this model, dexamethasone added to the drinking water of maternal rats both prepartum and postpartum resulted in a 50% greater survival rate of midbrain dopaminergic neurons in the adult offspring.[79] Such a model also provides a potential explanatory framework for the high comorbidity between major depression and substance abuse.

POSTMORTEM FINDINGS

Postmortem studies of the DA system in depressed patients are relatively few and not surprisingly have provided conflicting results, due at least in part to variability in age of the subjects, agonal states, presence of psychotropic medications, and the inclusion in some studies of victims of suicide, which may have its own unique pathobiology.[80] Brain concentrations of DA in suicide victims are unchanged compared with controls.[81-84] Homovanillic acid concentrations have been found to be elevated[84,85] or unaltered[86] in the frontal cortex and unaltered in the basal ganglia[83,84] of suicide victims. Cerebrospinal fluid HVA concentrations have been found to be lower in suicide attempters than controls[87] but not different between patients with a high- vs low-lethality attempt.[88] Concentrations of dihydrophenylacetic acid in the caudate, putamen, and nucleus accumbens were reduced in antidepressant-free depressed patients who died by suicide compared with controls.[89]

In one elegant postmortem study using immunohistochemical and autoradiographic methods with high anatomical resolution, depressed subjects, most of whom died by suicide, demonstrated reduced DAT density and elevated D_2/D_3 receptor binding in the central and basal nuclei of the amygdala compared with psychiatrically normal controls.[90] A second study using different methods found no difference in D_2 receptor number or affinity.[89] Neither of these studies reported a difference in D_1 receptor binding between depressed subjects who died by suicide and controls.[89,90]

NEUROIMAGING FINDINGS

Relatively few studies have examined DA system alterations in depression with neuroimaging methods. Published studies have focused largely on D_2 receptor or DAT occupancy. Interpreting results of earlier studies using [^{123}I]-2β-carboxymethoxy-3β-(4-iodophenyl) tropane (^{123}I-β-CIT) to image the DAT are problematic in that the binding profile for this ligand is not specific for this monoamine transporter, although in the striatum, the vast majority of binding is indeed to the DAT.[91] Few studies of DAT binding or uptake have been performed with more specific ligands.

Results of neuroimaging studies of D_2 receptor binding in major depressive disorder have been inconsistent (**Table 2**). Early studies found elevated striatal D_2 binding levels in depressed inpatients, either in whole group samples[92,93] or when limited to a psychomotor retarded group.[94] Elevated D_2 receptor binding may reflect increased numbers of D_2 receptors in depression, an increase in affinity of the receptor for the ligand, or a decrease in availability of synaptic DA (which competes with the radiolabeled ligand, albeit weakly, for D_2 binding). Two later studies failed to confirm these findings, although 1 study used a nonhealthy control group[95] and the other studied outpatients.[96] The subjects in this latter study were less ill than those in the previous studies and few had even moderate psychomotor retardation. A major confound across the studies was the medication status of the subjects, as most were either on antidepressant therapy or had only a 7-day washout prior to the imaging procedure. Variability in the level of anxiety may also confound the results, as anxiety has been associated with reduced D2 receptor expression.[101]

Conflicting results have also been found in other types of imaging studies (Table 2). In the 2 studies comparing D_2 binding before and after antidepressant treatment for depression, clinical improvement was noted with either an increase or decrease in D_2 receptor binding, perhaps due to the differing mechanism of action of the drugs used.[94,95] Studies of DAT expression have also found conflicting results, although the most comprehensive positron emission tomography study observed reduced DAT binding in depression.[98] In a positron emission tomography study assessing DA neuronal function by measuring [^{18}F]-fluorodopa uptake in the striatum, depressed patients with psychomotor retardation exhibited reduced striatal uptake of the radioligand compared with anxious depressed inpatients and healthy volunteers.[97]

CLINICAL THERAPEUTICS

Of the antidepressants either currently or previously available, those that are likely to enhance DA neurotransmission include nomifensine, a potent DA and NE reuptake

Table 2. Neuroimaging Studies of Dopamine Signaling in Major Depression

Source	Year	Subjects	Medication Status of Patients	Technique	Primary Findings
			D_2 Binding in Depressed vs Controls		
D'Haenen and Bossuyt[92]	1994	21 inpatients; 11 controls	≥7 d antidepressant washout	SPECT ^{123}IZBM	10% greater basal ganglia/cerebellum D_2 binding ratio in depressed patients (P=.03).
Shah et al[93]	1997	15 inpatients; 15 controls	8 receiving antidepressant; 7 unmedicated (duration of treatment not reported)	SPECT ^{123}IZBM	Depressed subjects demonstrated significantly greater D_2 binding in right striatum. Binding correlated with reaction time and verbal fluency.
Ebert et al[94]	1996	20 male inpatients; 10 male controls	10 unmedicated ≥6 mo; 10 receiving AMI for 2 wk	SPECT ^{123}IZBM	No difference among the 3 groups at baseline. Psychomotor retarded patients had 6% increase in striatal D_2 binding vs all others (P<.05).
Klimke et al[95]*	1999	15 inpatients (3 BP); 17 controls with melanoma	≥7 d antidepressant washout	SPECT ^{123}IZBM	No difference in striatal D_2 binding for whole group. At baseline, responders to SSRI treatment had significantly decreased D_2 binding vs nonresponders and controls.
Parsey et al[96]	2001	9 patients; 10 controls	≥2 wk antidepressant washout	SPECT ^{123}IZBM	No difference in striatal D_2 binding at baseline. No difference in striatal D_2 binding after amphetamine administration.
			Depressed Before and After Treatment		
Ebert et al[94]	1996	10 inpatients	Treatment with 150 mg AMI per day for 3 wk	SPECT ^{123}IZBM	Nonresponders to 3 wk of AMI showed increased or no change in striatal D_2 binding. Responders to AMI significantly decreased D_2 binding (P<.05).
Klimke et al[95]	1999	15 inpatients (3 BP)	Treatment with fluoxetine or paroxetine for 6 wk	SPECT ^{123}IZBM	After 3-7 wk of SSRI treatment: nonresponders had decreased D_2 binding in striatum;responders had increased D_2 binding in striatum and increased D_2 binding correlated with reduction in HAMD score.
			DAT Expression and Function		
Martinot et al[97]	2001	6 inpatients with PMR and AF; 6 inpatients with impulsivity/anxiety; 10 controls	3 patients in each group receiving an SSRI; 3 in each group unmedicated	PET [^{18}F]DOPA	Patients with PMR and AF had lower [^{18}F]DOPA uptake K_i values in left caudate than impulsive/anxious depressed or controls.
Meyer et al[98]	2001	9 patients; 23 controls	≥3 mo unmedicated with psychotropics	PET [^{11}C]RTI-32	Striatal DAT levels lower bilaterally in patients than controls. Patients with lower DAT levels performed better on finger tapping test and Stroop test.
Brunswick et al[99]	2003	15 patients (5 BP); 46 controls	≥7 d antidepressant washout	SPECT [^{99m}Tc]- TRODAT-1	DAT levels higher in bilateral putamen and left caudate in patients vs controls.

Abbreviations: ACC, anterior cingulate cortex; AF, affective flattening; AMI, amitriptyline; BP, bipolar depressed; DAT, dopamine transporter; [^{18}F]DOPA, [^{18}F]fluorodopa; D_2, dopamine receptor; HAMD, Hamilton Depression Scale; ^{123}IBZM, ^{123}I-iodobenzamide; K_i, inhibition constant; PET, positron emission tomography; PMR, psychomotor retardation; [^{11}C]RTI-32, [^{11}C]methyl (1R-2-exo-3-exo)-8-methyl-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate; SPECT, single-photon emission computed tomography; SSRI, selective serotonin reuptake inhibitor; [^{99m}Tc]TRODAT-1, technetium, 2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino]ethanethiolato(3-)-oxo-[1R-(exo-exo)].

*Klimke et al (1999) report updated results of their group's original publication (Larisch et al[100]).

inhibitor[102]; amineptine, a DAT antagonist; sertraline, an SSRI that also blocks DA reuptake at high doses; bupropion, although this remains controversial; and MAOIs, which prevent degradation of DA, NE, and 5HT. Moreover, the absence of DAT in the prefrontal cortex and the role of the norepinephrine transporter in inactivating the DA signal in this critical brain region, taken together, have revealed an effect of NE reuptake inhibitors to increase DA availability in this area.

Although bupropion is often considered to produce its antidepressant effects via DAT blockade, at clinically significant doses the drug occupies less than 22% to 26% of DAT binding sites.[103,104] In contrast, SSRIs typically inhibit 80% or more of serotonin transporter binding sites at minimally effective doses.[105] The greater efficacy of MAOIs over TCAs in atypical depression and anergic bipolar depression suggests that alterations in DA metabolism may be particularly important for these conditions.[106]

In addition, several drugs acting on the DA system have been evaluated for their efficacy in major depression. The first agents used to treat depression that directly altered dopaminergic signaling were the psychostimulants, acting through increases in DA release and blockade of the DAT, although these agents also act on 5HT and NE neurons. In double-blind, placebo-controlled studies of unselected depressed patients, psychostimulants are infe-

rior to TCAs and MAOIs.[107] Studies using methylphenidate or dextroamphetamine as a predictor of response to TCAs found inconsistent results, although design limitations likely contributed to these results.[108] Amineptine was approved for treatment of depression in France but later withdrawn due to problems with abuse of the drug.

Bromocriptine, a D_2 agonist, was found to be as efficacious as TCAs in depression in 3 small double-blind studies, although the absence of a placebo confounds interpretation of these findings.[109] Open-label studies suggest that bromocriptine may provide antidepressant benefit in treatment-resistant depression and tachyphylaxis-associated relapses.[110,111] In a small double-blind trial, the DA agonist piribedil was efficacious in depression with low pretreatment cerebrospinal fluid HVA concentrations predictive of response.[61] Pergolide, a DA agonist used for Parkinson disease, suggested efficacy in 2 open-label augmentation trials for major depression,[112,113] but a placebo-controlled augmentation study did not demonstrate benefit.[114]

Pramipexole, a nonergot DA agonist used in the treatment of Parkinson disease and restless legs syndrome, exhibits marked selectivity for D_2-like receptors, particularly the D_3 receptor. Several case series and reports suggested antidepressant efficacy for pramipexole in refractory bipolar depression[115,116] or as an augmentation agent with SSRIs, TCAs, or psychotherapy.[117-120] In a study of baboons, pramipexole reduced cerebral blood flow in the orbitofrontal cortex, subgenual anterior cingulate cortex, and insula, all regions thought to contribute significantly to mood regulation.[121] Three double-blind placebo-controlled trials have explored the use of pramipexole for the treatment of major depressive episodes. In unipolar depression, pramipexole (5 mg/d) was superior to placebo and equivalent to fluoxetine (20 mg/d) among completers of an 8-week trial.[122] Two studies of patients with bipolar depression on mood stabilizer therapy found significantly greater response rates in pramipexole- vs placebo-treated patients.[123,124] Augmentation of an SSRI or SNRI with an atypical antipsychotic also shows efficacy in partially responsive and nonresponsive depressed patients,[125] although whether this improvement occurs through changes in DA signaling is uncertain.[126]

In contrast to the depressive relapse induced by dietary depletion of tryptophan in SSRI responders or tyrosine depletion in TCA responders, dietary depletion of the DA precursors phenylalanine and tyrosine does not induce a recurrence in remitted depressed patients.[127,128] However, availability of these amino acid precursors to DA, unlike 5HT, are not rate-limiting in DA synthesis. Administration of α-methylparatyrosine, an inhibitor of tyrosine hydroxylase, rapidly reduces levels of catecholamine metabolites and induces a robust increase in depressive symptoms, particularly anhedonia, poor concentration, and loss of energy in patients treated with NE reuptake inhibitors.[129]

SEROTONIN-DOPAMINE INTERACTION

An important remaining question is how SSRIs and SNRIs alter, or fail to alter, DA systems. It is now clear that treatment with these antidepressants, although clearly superior to placebo treatment, frequently fail to render patients symptom free; ie, the majority do not achieve remission.[1] Such partial response may result from a failure of increased serotonergic or noradrenergic neurotransmission to induce similar alterations in DA signaling. Supporting this hypothesis is the finding that SSRI responders, but not nonresponders, exhibited increased DA binding to D_2 receptors in the striatum and that the degree of increase in D_2 binding correlated with improvement in Hamilton Depression Scale score.[94]

There is substantial interaction between the central nervous system serotonergic and dopaminergic systems with the DA cell bodies in the VTA and substantia nigra pars compacta being targets for the serotonergic cells of the midbrain raphe.[130] In addition, $5HT_{1A}$ receptor activation stimulates DA release in the prefrontal cortex and nucleus accumbens but may inhibit DA release in the dorsal striatum. Activation of $5HT_{2C}$ receptors inhibits mesocortical and mesolimbic DA function.[131,132] In the brainstem raphe cells, firing of serotonergic neurons reduces spontaneous activity of DA neurons in the VTA, but not the substantia nigra pars compacta, and inhibits DA-related behaviors, such as locomotor and exploratory behavior.[133,134] Chronic treatment with serotonergic antidepressants may induce a down-regulation of the $5HT_{2B/2C}$ receptors on VTA dopamine neurons believed to mediate this effect and thus may contribute to amelioration of DA-related depressive symptoms.[135]

CONCLUSIONS

The question of what, if any, role DA circuit dysfunction plays in the pathophysiology of depression remains an open one. Several directions for future research are identified by this review. The most fruitful investigations may be with subjects nonresponding or nonremitting with existing treatments, including those with bipolar depression. Strategies combining pharmacologic challenges with neuroimaging of subjects, both at rest and while engaged in DA-related tasks, such as reward processing, would be highly informative. Pretreatment and posttreatment studies could identify state vs trait disturbances in DA signaling. Clinical trials with pure-DA acting compounds as monotherapy and for augmentation in SSRI/SNRI nonresponders would also be valuable. Further elucidation of the role of DA dysfunction is clearly warranted as psychiatry strives to find ways to improve outcomes of patients with depressive disorders.

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