Role of the Dopaminergic System in Depression

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A hypothesis implicating dopamine in depression was proposed over 15 years ago (Randrup et al 1975). The identification of multiple new subtypes of dopamine receptors and evolving views regarding the function of the dopamine systems in the brain require a reexamination of this hypothesis. Results from studies in depression, Parkinson's disease, and animal models of depression suggest a deficiency of dopamine in depression. Dopamine precursors, dopamine agonists, and dopamine reuptake inhibitors show therapeutic efficacy in depression. Electroconvulsive therapy (ECT) and standard pharmacological antidepressants enhance dopamine function. Studies using receptor-specific drugs in clinical trials and neuroimaging studies are needed to further clarify the role of dopamine in depression.

Introduction

The catecholamine and indoleamine hypotheses of depression (Schildkraut 1965; Lapin and Oxenkrug 1969) spurred research into abnormalities of noradrenergic and serotonergic transmission as causes of depression. Subsequently a dopamine hypothesis of depression was put forward (Randrup et al 1975). Since then, multiple lines of investigation have explored the role of dopaminergic systems in depression. In this article we outline the neuroanatomy and neurochemistry of the dopamine system with special emphasis on newer information, and then review animal and human research regarding the involvement of dopamine in depression and antidepressant action.

Dopamine System

The dopaminergic systems in the brain arise from groups of cells in the midbrain and the hypothalamus. The midbrain cells are clustered into three distinct groups—A8 in the retro-rubral field, A9 in the substantia nigra, and A10 in the ventral tegmental area. Neurons arising in areas A8 and A9 ascend to the striatum and are called the nigrostriatal pathway. These neurons contain 70% of brain dopamine and are involved in the modulation of motor behavior. Neurons ascending from area A10 project to the limbic areas (nucleus accumbens, olfactory tubercle, septum) and cortical areas (cin-
gulate, entorhinal, prefrontal, and pyriform cortices) and are called mesolimbic and mesocortical pathways, respectively. These neurons are involved in cognition and modulation of behaviors linked with motivation and reward (Creese 1985; Roth et al 1987). Evidence from the studies of neuroanatomical substrates of animal behavior and the animal models of psychiatric illness, suggests that the mesolimbic dopaminergic system may be involved in the pathophysiology of schizophrenia, affective disorders, and substance abuse (Willner 1991). Four discrete groups of dopaminergic cell bodies have been identified in the hypothalamus, which project to the median eminence and the neurohypophysis, and are involved in the neuroendocrine regulation of prolactin secretion (Creese 1985; Moore 1987).

The effects of dopamine in the Central Nervous System (CNS) were initially considered to be mediated via two receptor subtypes D₁ and D₂. The D₁ receptors activate the adenylate cyclase system and the D₂ receptors inhibit it. D₁ receptors are localized postsynaptically. D₂ receptors are localized both presynaptically and postsynaptically, with the presynaptic receptors functioning as inhibitory autoreceptors (Andersen et al 1990). Initially only D₂ receptors had identifiable effects in the based CNS, based on the action of D₂ antagonists, which are effective as antipsychotics and cause extra pyramidal symptoms. However, recent behavioral studies using selective agents have shown that D₁ receptors may play an important role in the expression of the effects of the dopaminergic system (Kingston et al 1988). Moreover, studies with agonists reveal the existence of high affinity and low affinity forms for both D₁ and D₂ receptors, and it is the high affinity conformation that is coupled to the second messenger system (Arnt and Hyttel 1988; Beart 1989). Previous studies of receptor binding have generally not quantitated the proportion of receptors in the high affinity state, thus valuable data are missing from most previous studies.

Developments in molecular genetics and cloning techniques have assisted in the further dissection of dopamine receptor subtypes. Genes for D₁ and D₂ receptors have been cloned (Strange 1991). Analysis of the intron-exon structure of the D₂ receptor gene reveals subtypes on the basis of alternative splicing (Anderson et al 1990). Recently, genes for three other dopamine receptor subtypes have been cloned (Sokoloff et al 1990; Sunahara et al 1991; Van Tol et al 1991). The D₃ receptor has been cloned and characterized. It is structurally similar to the D₂ receptor, is found both presynaptically and postsynaptically, but is localized to the limbic areas of the brain (Sokoloff et al 1990). The D₄ receptor has been cloned. It is pharmacologically similar to the D₂ and D₃ receptor, is localized to the limbic areas and has a higher affinity for clozapine (Sunahara et al 1991). In addition, an adenylate cyclase-linked dopamine receptor, D₅, is localized to the limbic system, has strong homology and pharmacological similarity to D₁ but a higher affinity for endogenous dopamine (Van Tol et al 1991). It is clear that the dopamine receptors are more heterogeneic in structure and function than was initially presumed, therefore, all previous biochemical and behavioral studies have to be reevaluated in light of the emerging subtypes of dopamine receptors.

Role of Dopamine in Depression

The relationship of dopamine and depression has been studied from various perspectives. We summarize results from four major lines of investigation and present the conclusions.
Animal Studies of Depression

Because the main constructs used to define depression in humans are depressed mood and anhedonia, it is difficult to establish the validity of animal models as being representative of the human condition (Willner 1984). Yet, animal models offer opportunities for much greater experimental control and direct access to the brain and hence may be useful in generating testable hypotheses of depression (Henn 1989). Animal studies investigating the role of dopamine in depression have used three approaches: (1) alterations in the dopamine system in animal models of depression; (2) the role of dopamine in behaviors assumed to have relevance to human depression such as motivation and reward seeking; (3) the effects of drugs that affect the dopamine system on animal behavioral models of depression.

“Learned helplessness” is a commonly used animal model of depression wherein animals exposed to inescapable stressors exhibit decreased spontaneous activity, decreased effort to escape, and a variety of somatic changes, which are reversed specifically by antidepressants (Sherman et al 1982). Dopamine depletion in the caudate nucleus and the nucleus accumbens occurs in animals with “learned helplessness” (Anisman et al 1979a; Anisman et al 1979b). Prior treatment with a dopamine agonist prevents the development of the learned helplessness state (Anisman et al 1979a; Anisman et al 1979b). Conversely, dopamine antagonists exacerbate learned helplessness and prevent the improvement produced by antidepressant treatment (Muscat et al 1990).

“Behavioral despair” or the “forced swim test” is another model in which rats are forced to swim in a confined space. After initial attempts to escape they assume an immobile posture. Similar to their ameliorative effect in the learned helplessness model, antidepressants exert an antiimmobility effect. Dopamine agonists augment the antiimmobility effect and the dopamine antagonists reverse it (Borsini and Meli 1990). Thus, although there is evidence for a role of dopamine in these animal models of depression, a significant issue is that these models have limited validity (Willner 1984; Henn 1989).

Another approach is based on the assumption that depression involves neurobiological alteration in the central reward-seeking, motivation, and environmental responsivity mechanisms, leading to anhedonia, social isolation, and psychomotor retardation, the core symptoms of depression (Wise 1989; Fibiger et al 1990; Willner 1991). Studies have investigated the role of the mesolimbic dopaminergic system in the maintenance of the reward response. Experiments using drug self-administration paradigms have shown that the self administration of drugs that possess reinforcing properties such as narcotics, nicotine, cocaine, and psychostimulants, are associated with an increase in the firing of dopaminergic neurons in the A10 nuclei, activation of the mesolimbic pathways, and an increase in the extracellular concentration of dopamine in the nucleus accumbens (Di Chiara et al 1990; Pulvirenti and Koob 1990). Similarly, studies of intracranial self-stimulation show that electrodes placed in the A10 nuclei support high rates of self-stimulation, which are accompanied by an activation of the mesolimbic pathway and dopamine release within the nucleus accumbens and is abolished by lesions of the nucleus accumbens (Wise 1989). Although these studies support the involvement of dopamine in these specific behaviors, there is no consensus as to whether these behaviors represent reward, reinforcement, behavioral activation, incentive motivation, or psychomotor stimulation, even less clear, is what implications these findings have for human depression (Willner 1991; Henn 1989; Wise 1989).
Human Studies of Depression

Studies of the synthesis, storage and catabolism of dopamine have not identified a consistent abnormality in patients with depressive disorders (Willner 1983a). The functional status of the dopaminergic system has been assessed by measuring the responsivity of dopamine receptors to dopamine agonists as reflected in suppression of levels of prolactin and increase in growth-hormone levels. Most neuroendocrine studies do not find a functional abnormality in the dopaminergic function in depression (Balldin et al 1982; Christie et al 1982; Costain et al 1982).

The most consistent finding in human studies is decreased turnover of dopamine in patients with depressive disorders. Homovanillic acid (HVA) is the major metabolite of dopamine, and almost all cerebrospinal fluid (CSF) HVA originates from the brain. Thus, CSF HVA reflects CNS dopamine turnover. Studies have used probenecid to block the transport of HVA from the CSF, to increase the validity of CSF HVA as a measure of CNS dopamine turnover. Most studies have found a decrease in the CSF HVA of patients with depression. The results are more striking when probenecid is co-administered and the differences are most pronounced in a subgroup of patients with psychomotor retardation (Papeschi and McClure 1971; van Praag and Koff 1971; Goodwin et al 1973; Randrup et al 1975; van Praag et al 1975). However, other studies that have failed to replicate these findings or have found an increased CSF HVA in patients with depression (Jimerson 1987; Vestergaard et al 1978). Some authors contend that the decrease in CSF HVA may be secondary to the psychomotor retardation rather than being a part of the pathogenesis of depression (Post et al 1973; Randrup et al 1975; van Praag et al 1975). Therefore, although there is considerable evidence that CSF HVA may be lower in depression, it is not clear whether this is a primary abnormality or whether it is secondary to psychomotor retardation.

Effects of Dopamine Depletion or Blockade of Dopamine Receptors

Reserpine, a rauwolfia alkaloid used as an antihypertensive, produces a syndrome marked by behavioral sedation in animals and is associated with a higher incidence of depression-like syndrome in humans. Goodwin and Sack (1974) suggest that reserpine only precipitates depression in patients with a predisposition to affective illness rather than causing it de novo, and others contend that the reserpine-induced syndrome is not the same as depression but represents drug-induced psychomotor retardation (Bein 1982; Mckinney and Kane 1967). Alpha-methylldopa, an antihypertensive that displaces dopamine from its vesicles and may act as a false neurotransmitter in the noradrenergic and dopaminergic systems, is also associated with a higher incidence of depression (Mckinney and Kane 1967; Randrup et al 1975; Willner 1983a). Moreover, a syndrome of depressive symptoms has been observed in patients who stop chronic sympathomimetic abuse suddenly, and some authors have suggested that this may involve the dopaminergic system (Groves et al 1990; Pulvirenti and Koob 1990).

Neuroleptic agents block the dopamine receptors and decrease CNS dopaminergic transmission. Some studies report depression as a side effect of neuroleptics (Randrup et al 1975). Neuroleptics are ineffective and may even worsen depression with psychomotor retardation, a subgroup of patients found to have decreased dopamine turnover (Raskin et al 1970; Randrup et al 1975; Raskin and Crook 1976; Willner 1983a). However, other studies point to the antidepressant effect of neuroleptics (Robertson and Trimble 1982).
and that neuroleptics are useful in patients with depression accompanied with agitation or psychotic features, a subgroup of patients reported to have an increased CSF HVA (Sweeney et al 1978; Aberg-Wistedt et al 1985; Agren and Terenius 1985). Dopamine depletion or receptor blockade may produce symptoms seen in depression or even a full-blown depressive syndrome. Nevertheless, it is difficult to determine why only some patients experience these behavioral effects.

Parkinson’s Disease

Parkinson’s disease is an idiopathic disorder characterized by rigidity, akinesia, and tremor and is associated with degeneration of the nigrostriatal dopaminergic system and loss of projections of the midbrain limbic and cortical projections (Cummings 1985). The incidence of depression in Parkinson’s disease (about 40–50%) is higher than in healthy controls (about 3–5%) (Cummings 1985; Mayeux 1990). Gotham et al (1986) suggest that an increased incidence of depression can be attributed solely to the disabling effects of chronic illness. However, the emergence of depression before the onset of motor symptoms of Parkinson’s disease, the lack of relation between the severity of Parkinson’s disease and depression; and the higher incidence of depression in Parkinson’s disease even when compared with patients with equally disabling illnesses argues against a “reactive” etiology of depression in Parkinson’s disease (Cummings 1985; Mayeux 1990).

Although a role for dopamine in Parkinson’s disease is established and a neurobiological contribution to the pathogenesis of depression in Parkinson’s disease seems likely, a direct relation between dopamine and depression in Parkinson’s disease has been harder to establish. Depression in Parkinson’s disease does not correlate with CSF HVA levels (Mayeux 1990). L-dopa which treats the motor components of Parkinson’s disease, does not always alleviate depression in these patients; conversely antidepressants often improve the mood without a change in the motor component of the disease; and electroconvulsive therapy (ECT) improves both (Andersen et al 1980; Cummings 1985; Andersen et al 1987; Douyon et al 1989; Mayeux 1990). Alteration in the serotonin function is becoming increasingly evident in depressed patients with Parkinson’s disease (Mayeux 1990). Thus, it appears that although dopamine degeneration may be a link in the casual chain of depression, it may not be solely responsible for the mood alterations seen in Parkinson’s disease.

The Antidepressant Effects of Dopaminergic Agents

Dopamine Precursors

Tyrosine, an amino acid, is converted to dihydroxyphenylalanine (dopa), which in turn is converted to dopamine by L-aromatic acid decarboxylase. In noradrenergic neurons the enzyme dopamine-β-hydroxylase converts dopamine to norepinephrine. Under basal conditions, the exogenous administration of tyrosine leads to a rather specific enhancement of norepinephrine without much effect on the dopaminergic transmission (Gelenberg et al 1982). However, under conditions of dopamine deficiency, tyrosine causes an enhancement of dopaminergic transmission and has been tried as an antidepressant in one controlled and one uncontrolled study and found to be useful (Gelenberg et al 1982). Mouret et al (1988) claim to have identified a subset of depressed patients on the basis of their rapid eye movement (REM) sleep patterns who respond to oral L-Tyrosine with
a mood elevation within a day along with a reversal of their sleep abnormalities. These preliminary studies need to be replicated.

Several studies have explored the antidepressant efficacy of L-dopa in depression, with or without a peripheral decarboxylase inhibitor. Although it is evident that L-dopa has definite effects on mood, its antidepressant efficacy in an unselected population is unimpressive (Goodwin and Sack 1974; Randrup et al 1975; Gelenberg et al 1982; Willner 1983a). L-dopa may display greater efficacy as an antidepressant in a subset of patients with psychomotor retardation or with a low pretreatment CSF HVA (Goodwin and Sack 1974; van Praag et al 1975; Gelenberg et al 1982). Apart from the improvement observed in depressions, psychomotor activation was observed in the majority of patients. In unipolar depressed patients who did not improve, increased agitation and emergence of psychotic features was seen and hypomania was noted in patients with bipolar disorder (Goodwin and Sack 1974).

The efficacy of L-dopa in the treatment of depression in patients with Parkinson’s disease is unclear. Although improvement in depression has been observed in patients receiving L-dopa, an induction of depression has also been documented on initiation of L-dopa in patients with Parkinson’s disease (Gelenberg et al 1982; Mayeux 1990). Moreover, since L-dopa is an effective treatment for the motor disabilities of Parkinson disease, it is hard to distinguish whether the improvement that is seen in the depression of these patients is an effect of enhanced dopaminergic transmission on the neurobiology of depression or if it represents a “reactive” improvement secondary to the alleviation of the motor deficits.

Dopamine Agonists

Amphetamine promotes the release of norepinephrine and dopamine from the nerve terminals and inhibits their reuptake. Because the euphoriant effect of amphetamine is blocked by pimozide, a dopamine antagonist, and not by alpha-adrenergic or beta-adrenergic blocking agents, the behavioral effects of amphetamine appear to be mediated by the dopaminergic system (Randrup et al 1975; Willner 1983a). Infusion of amphetamine in patients with depression leads to a transient decrease in psychomotor retardation and social withdrawal followed by intense fatigue and a rapid development of tolerance (Randrup et al 1975; Willner 1983a). Bipolar depressed patients usually report euphoric feelings, whereas unipolar depressed patients reported effects ranging from euphoria or no change to dysphoria (Silberman et al 1981). The effects of amphetamine suggest that the role of dopamine in mood modulation may vary with the subtype of the affective illness.

Bromocriptine, an ergot alkaloid derivative, has significant dopamine agonist properties and is used as a standard treatment in Parkinson’s disease and as an inhibitor of prolactin secretion in galactorrhea (Fuxe et al 1978). Controlled studies of bromocriptine have only been undertaken in patients who are refractory to standard treatment and report antidepressant efficacy comparable to standard tricyclic antidepressants (Theohar et al 1981; Wæhrens and Oulach 1981; Wells and Marken 1989). This effect was seen in depressed patients classified as “psychogenic” as well as “endogenous” (Theohar et al 1981). As noted with dopamine precursors, tyrosine and L-dopa, bromocriptine produced an earlier response than standard tricyclics and was associated with a higher incidence of psychomotor activation and precipitation of mania (Theohar et al 1981; Silverstone 1984).

Piribedil, a piperazine derivative, is predominantly a dopamine agonist with little effect
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on the noradrenergic or serotonergic system (Post et al 1973; Creese 1974). At low doses, piribedil stimulates the presynaptic autoreceptors leading to functional dopaminergic antagonism and at higher does it directly stimulates the postsynaptic receptors and acts as a functional dopamine agonist (Post et al 1978). In doses in which it is mainly a presynaptic autoreceptor agonist and hence a functional dopamine antagonist, piribedil was an effective treatment for the acute episode of mania in two cases (Post et al 1976). Conversely, in doses in which piribedil acts as a functional dopamine agonist, it has been found to exert an antidepressant effect (Post et al 1978). Consistent with observations of other dopamine enhancing drugs, it was most effective as an antidepressant in the subset of patients with low CSF HVA and has been reported to switch a depressed patient with bipolar illness into mania (Post et al 1976; Post et al 1978). A more recent open study reports that in a subset of depressed patients with characteristic polysomnographic and clinical features, piribedil and other dopamine agonists, cause a rapid and complete reverse of depression with a normalization of polysomnographic features (Mouret et al 1987).

L-Sulpiride is a selective D2 antagonist. It preferentially blocks presynaptic autoreceptors at lower doses and inhibits feedback resulting in an increased dopamine turnover, although at higher doses it blocks the postsynaptic D2, increases prolactin levels, and functions like a classical neuroleptic (Serra et al 1990). The antidepressant efficacy of low doses of L-sulpiride has been demonstrated in double-blind placebo-controlled trials, and in comparative trials, it displays efficacy equal to that of amitriptyline (Del Zompo et al 1990; Standish-Barry et al 1983).

**Dopamine Reuptake Inhibitors**

Nomifensine is a tetrahydroisoquinolone derivative that inhibits the reuptake of dopamine and norepinephrine and may even have direct agonist activity (Kinney 1985). Studies using in vivo brain microdialysis show an increase in the dopamine release from the striatum in rats (Butcher et al 1991). Animal studies reveal that nomifensine increases stereotypy and circling behaviors similar to amphetamine and apomorphine, which further attest to its dopaminergic profile (Costall and Naylor 1977). Neuroendocrine studies with nomifensine in humans are compatible with its effect on norepinephrine and dopamine reuptake and a direct agonist effect (Scheinin et al 1987). A recent positron emission tomography (PET) study in primates and humans using 11C-nomifensine demonstrates that nomifensine has a high affinity and specificity for the dopamine reuptake sites in vivo (Aquilonius et al 1987).

Clinical studies of the efficacy of nomifensine have consistently demonstrated antidepressant efficacy. Over 20 double-blind placebo-controlled or active drug-comparison studies found that nomifensine is superior to placebo and equivalent to standard treatments such as amitriptyline, imipramine, maprotiline, zimelidine, clomipramine, and mianserin (Forrest et al 1977; Grof et al 1977; McClelland et al 1977; Kinney 1985). In most studies nomifensine is either nonsedating or activating. VanScheyen et al (1977) observed that the motor-retardation responds more to nomifensine as compared to other antidepressants and the levels of CSF HVA amongst nomifensine-responders are significantly lower. Some authors have cautioned against the use of nomifensine in patients with agitated or psychotic depression because of the concern that the agitation or the psychosis may worsen, an effect seen with amphetamine-like drugs (Kinney 1985). In its specific effect on psychomotor retardation, greater efficacy in patients with low CSF HVA and potential for worsening agitation and psychosis, nomifensine resembles other dopaminergic agents,
arguing for the role of its dopaminergic action in its antidepressant effect. It should be noted that nomifensine is not longer marketed because it causes hemolytic anemia, an effect unrelated to its dopaminergic action.

Bupropion has been studied extensively in clinical trials and found to be superior to placebo and comparable to standard antidepressants, although as yet no specific subpopulation of depressed patients who respond preferentially to bupropion has been identified (Settle 1989; Zung 1983). Bupropion, a unicyclic aminoketone, structurally resembles two sympathomimetic compounds, diethylpropion hydrochloride and amphetamine, both with prominent dopaminergic activity (Golden et al 1988). In aminal studies, it is a dopamine reuptake-inhibitor and does not alter the release of biogenic amines or have an effect on the monoamine oxidase (Ferris et al 1983). In vivo brain microdialysis studies in freely mobile rats show that bupropion increases the dopamine concentration in the striatum and the nucleus accumbens without an appreciable effect on the serotonin and norepinephrine systems and that the increase in dopamine concentration is temporally associated with an increase in dopamine-associated stereotypic and locomotor behaviors (Nomikos et al 1989). However, in animal models of depression the dose of bupropion required to produce a maximal antidepressant effect is one-seventh that required to produce dopamine reuptake blockade (Golden et al 1988). Moreover, subsequent studies have revealed that bupropion has several active metabolites, which differ by species, and at this time the contribution of bupropion and its metabolites to its pharmacological actions is unclear (Martin et al 1990). Thus, while bupropion is an effective antidepressant and has a prominent effect on the dopaminergic system, the relationship of the two properties needs further clarification.

L-Deprenyl (selegiline) is propargylamine derivative that forms an irreversible covalent bond with the monoamine oxidase subtype B (MAO-B). MAO-B is the predominant form of the enzyme in the human brain and dopamine and phenylethylamine are its preferred substrates, whereas norepinephrine and serotonin are the preferred substrates for monoamine oxidase A (MAO-A). The selectivity of the drug for the MAO-B subtype is dose-dependent and at higher doses (>20 mg/day) it becomes nonselective and also inhibits MAO-A (Kabins and Gershon 1991; Knoll 1983). The overall effect of the drug is to cause a slight but significant increase in the levels of DA content in the nigro-striatal system and an enhanced sensitivity of the dopaminergic neurons to physiological and pharmacological influences (Knoll 1983).

Multiple open antidepressant trials of deprenyl have been conducted. Some report antidepressant efficacy at a selective, less than 15 mg/day dose, although others show efficacy only at nonselective doses (Mann et al 1989). In these studies a trend was noted towards a better response in patients with nonendogenous and bipolar depression (Mann et al 1982). Using a double-blind placebo-controlled design, Mendis et al (1981) reported no antidepressant effect of 20 mg/day for 3 weeks, whereas Mendelwicz and Youndim (1983) reported an antidepressant effect of 15 mg/day in a 6-week trial. Mann et al (1989) found no antidepressant effect with the MAO-B selective dose after 3 weeks of treatment but found an antidepressant effect in the same patients when the dose was increased to the nonselective range and/or continued to a total of 6 weeks of treatment. These studies still leave unresolved the issue whether deprenyl is an effective antidepressant at a MAO-B selective dose if given for a 6-week trial (Mann et al 1989). If such efficacy can be demonstrated it would be further evidence in support of the relevance of dopaminergic mechanism for the antidepressant effect.

New drugs with greater receptor specificity are becoming available. Alpha-amineptine,
an antidepressant recently introduced in Europe, is unique in that it selectively inhibits the dopamine (DA) reuptake (Ceci et al 1986; Bonnet et al 1980). Large scale double-blind random-assignment trials in Europe have confirmed the efficacy of amineptine in the treatment of depression in all age-groups and subtypes of depression (Kemali 1989; Mendis et al 1989; Paes de Sousa and Tropa 1989). Early results also suggest a preferential response in patients with psychomotor retarded depression (Rampello et al 1991). New compounds, GBR-12935 and GBR12909, are highly selective dopamine reuptake blockers, show evidence of antidepressant activity in preclinical models, and are in various stages of clinical trials (Nielsen and Anderson 1990).

**Dopaminergic Effect of Antidepressant Agents**

In the previous section the antidepressant effect of diverse biochemical treatments that enhance dopaminergic transmission was studied. In this section we examine standard antidepressants, which do not primarily affect the dopaminergic system and discuss their effects on the dopaminergic system.

**Electroconvulsive Therapy**

As a non-pharmacological treatment, ECT is a powerful tool with which to investigate the biochemical effects that accompany antidepressant response. Spontaneous locomotor activity and stereotypic behaviors in rats are mediated by the mesolimbic and nigrostriatal pathways, respectively and increase in response to dopaminergic agents (Willner 1983b). Chronic, not acute, treatment with electroconvulsive shock consistently potentiates the dopaminergic activation of these behaviors (Green et al 1977; Green and Deakin 1980b; Deakin et al 1981; Wielosz 1981; Gulati et al 1987). In vivo microdialysis studies in rats find a multiple fold increase in the levels of dopamine in the striatum after electroconvulsive shock (ECS) (Nomikos et al 1991). In humans, prolactin and growth hormone release in response to dopamine receptor agonist apomorphine allow the study of dopamine receptor responsivity. Of the studies of growth hormone release in response to an apomorphine challenge, only one, Costain et al (1982), out of three found evidence of enhanced dopaminergic function after ECT (Balldin et al 1982; Christie et al 1982; Costain et al 1982). No studies of prolactin release found evidence to suggest increased dopaminergic transmission after a clinically successful course of ECT (Balldin et al 1982; Christie et al 1982). The efficacy of ECT in Parkinson's disease suggests an increase in dopaminergic function is produced but neuroendocrine studies do not confirm this (Balldin et al 1982; Christie et al 1982; Costain et al 1982; Fochtmann 1988; Douyon et al 1989).

Bolwig et al (1977) suggest that the increased effects of dopamine agonists seen in animal studies are related to the disruption of the blood–brain barrier permitting an increased dopamine access to the CNS sites. This hypothesis is supported by recent radiolabeled 3H-dopamine studies in animals that demonstrate increased penetrance of this compound, which does not cross the blood–brain barrier under normal circumstances, after a course of ECS (Gulati et al 1987). Some authors have ascribed the increase in dopaminergic effect after ECS to decreased autoreceptor sensitivity (Chiodo and Antelman 1980; Serra et al 1981), however others have been unable to confirm these effects (Green et al 1980a; MacNeil and Gowr 1982; Welch et al 1982). Studies of the effects of ECS in rats on the D₂ receptor binding using 3H-spiroperidol find no
increase in the number and affinity of these receptors (Bergstrom and Kellar 1979; Atterwill 1980), though a recent autoradiographic study reveals a localized increase in the nucleus accumbens, olfactory nuclei, and the amygdaloid nuclei (Barkai et al 1990). Studies using selective ligands for the D2 receptor find an increase in the receptor number in localized areas of the brain and in the second messenger response (Fochtmann 1988; Newman et al 1989; Barkai et al 1990). Adenylate cyclase activity following forskolin stimulation of Gpp(NH)p stimulation is increased (DeMontis et al 1990). Direct application of the second messenger, dibutyril cyclic adenosine mono phosphate (AMP), to the nucleus accumbens in animals treated with chronic ECS results in enhanced dopaminergic behaviors (Heal and Green 1978). This suggests the possibility that changes distal to the postsynaptic receptors in the dopaminergic system may be responsible for the enhanced response to dopaminergic agents (Heal and Green 1978; Barkai et al 1990). Thus, while the enhancement of dopaminergic function by ECS seems well established, the site of change and the relevance of this change to the antidepressant effect remain to be clarified.

Pharmacological Antidepressants

It has been observed that antidepressants with diverse pharmacological actions cause a decrease in the number and responsivity of beta-adrenergic receptors and/or a decrease in the number of serotonin 5-HT2 receptors, suggesting that these actions are related to antidepressant effect (Peroutka and Snyder 1980). Similarly, an effort has been made to identify effects on the dopaminergic system that cut across pharmacological classes (Willner 1983b). Multiple studies confirm the potentiation of the dopamine-agonist induced spontaneous locomotor behavior in animals treated chronically with tricyclics and atypical antidepressants like iprindole and mainserin (Spyraki and Fibiga 1981; Willner 1983b; Klimek et al 1985). In the same experiments, no increase has been seen in the stereotypy induced by dopamine-agonists (Spyraki and Fibiga 1981; Serra et al 1990). This has led to the suggestion that antidepressants increase sensitivity to dopaminergic agents in the mesolimbic pathways without affecting the nigrostriatal pathway, unlike ECS, which tends to increase sensitivity in both pathways (Spyraki and Fibiga 1981).

The question is how does this enhancement of dopaminergic responsivity take place? It has been suggested that the enhanced dopaminergic effects represent diminished sensitivity of dopaminergic presynaptic autoreceptors (Chiodo and Antelman 1980; Klimek et al 1985; Serra et al 1981), however, subsequent studies have failed to confirm these findings (Diggory et al 1984; Spyraki et al 1981). In a series of experiments Serra et al (1990) have shown that the potentiation of dopamine-mediated behaviors by chronic antidepressant treatment is mediated via an increased responsiveness of the postsynaptic D2 receptors in the mesolimbic system. However, studies of the D2 postsynaptic receptors using 3H-spiroperidol have consistently found no effect of chronic treatment with a variety of antidepressants (Klimek et al 1985; Peroutka and Snyder 1980; Willner 1983b). Given the enhancement of dopaminergic responses but no change in dopamine turnover, autoreceptors or postsynaptic D2 receptor, the alteration in D2 responsivity may be induced via a change in the facilitative actions of D1 receptor or at a site distal to the receptors within the second messenger pathway (Heal and Green 1978; DeMontis et al 1990; Serra et al 1990).
Conclusion

Lower CSF HVA levels in patients with depression, increased incidence of depression in Parkinson's disease and the depressant effects of dopamine-depleting agents or dopamine antagonists, all suggest that an impairment of the dopaminergic system may be associated with depression. Agents that enhance dopaminergic transmission exert an antidepressant effect, and antidepressants of biochemically unrelated classes as well as ECS, enhance dopaminergic effects in animal experiments. Pharmacological antidepressants improve depression and have no effect on the motor components of Parkinson's disease. In contrast, ECS, improves depression as well as the motor deficits of Parkinson's disease. Pharmacological antidepressants increase dopaminergic transmission only in the mesolimbic pathways, whereas ECS enhances dopaminergic transmission in both the mesolimbic and the nigro-striatal pathways; suggesting that increased dopaminergic transmission in the mesolimbic system is probably related to the antidepressants effects, although increased dopaminergic transmission in the nigro-striatal pathways is responsible for improvement of motor symptoms of Parkinson's disease.

Three new lines of investigation seem to be particularly promising for shedding light on the role of dopamine in depression. First, developments in molecular neurobiology in the last few years have greatly enhanced our understanding of the dopamine system and led to the discovery of new dopamine receptor subtypes. Although no studies have as yet investigated the role of D3–D5 in animal models or humans, given the localization of these newly cloned receptors within the limbic system it is likely that these receptors play a pivotal role in cognition, emotion, and antidepressant action of drugs and ECT. Development of more selective agonists and antagonists of D3–D5 receptors may uncover more specific antidepressants and antipsychotics. Because dopamine receptors display far more heterogeneity than initially presumed, all previous biochemical and behavioral studies have to be reevaluated in light of the emerging subtypes of dopamine receptors. The pathophysiology of depressive illness and the action of antidepressants may involve the newer subtypes of dopamine receptors. Second, nomifensine, bupropion and deprenyl, antidepressants with predominantly dopaminergic activity, all have effects on other neurotransmitter systems and thus leave open the question of the role of dopamine in antidepressant activity. Newer agents that have a selective and a specific effect on the dopaminergic system are becoming increasingly available and will help define further the role of dopamine in the antidepressant action.

The role of dopamine in the etiology of depression requires more direct confirmation than that provided by the study of antidepressant drugs. Rapid developments in the application of PET technology to the study of the DA system promise to yield direct evidence regarding the involvement of dopamine in depression. Specific ligands for the study of D1 and D2 receptors have been developed, the specificity of these ligands and their agreement with in vitro studies is acceptably high (Perlmutter et al 1991; Sedvall 1990). Probes are being developed to study dopamine synthesis, turnover, and uptake by the dopamine transporter as well as interactions with other neurotransmitters (Kilbourn et al 1989; Melega et al 1989; Barrio et al 1990; Dewey et al 1990). PET studies in schizophrenia and other neuropsychiatric syndromes have already shown correlation between DA activity in the brain and neuropsychological, cognitive, and affective variables. Although no PET studies of the role of dopamine in depression are available, the use of neuroimaging before, during, and after treatment of depression will help in resolving
whether dopamine changes are primary or secondary to depression, the relationship of dopamine changes to alterations in other neurotransmitter systems and the relationship of antidepressant action to changes in the dopaminergic system.

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References


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