Reevaluation of the Mesolimbic Hypothesis of Antipsychotic Drug Action

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Abstract

Conventional neuroleptic drugs are thought to derive their antipsychotic efficacy through influences on the mesolimbic dopamine (DA) system. In contrast, motor side effects of these drugs are suggested to follow from influences on the nigrostriatal DA system. This conceptualization is based on the assumption that behaviors mediated by the mesolimbic DA system are involved in schizophrenia while behaviors controlled by the nigrostriatal system are not. In this article, it is argued that although assumptions about mesolimbic activities may indeed be correct, those concerning the nigrostriatal system certainly are not. This being the case, drugs with mesolimbic-specific activity may not have significant antipsychotic potency and probably will not be free of motor side effects. The current thrust of neuropharmacology, which emphasizes development of drugs with pharmacological specificity rather than anatomical selectivity, is more likely to generate new antipsychotic agents with a reduced risk of motor side effects.


It is widely believed that neuroleptic drugs achieve their antipsychotic actions through influences on the mesolimbic dopamine (DA) system, while side effects, ranging from extrapyramidal signs to tardive dyskinesia, are attributed to drug actions in the striatum (e.g., Koob and Swerdlow 1988; Grace 1992; Laruelle et al. 1992; Schwartz et al. 1992; Sibley and Monsma 1992). First suggested in the early 1970s (Anden 1972; Matthysse 1973; Stevens 1973), the ideas central to this hypothesis remain essentially unchanged. For example, Grace (1992), in discussing the electrophysiological effects of neuroleptics, stated that the clinical profile of the response to antipsychotic drugs appears to correspond to the dopamine system affected: antipsychotic drugs that exert therapeutic actions in schizophrenics inactivate dopamine neuron firing in the limbic-related ventral tegmental area, whereas drugs that precipitate extrapyramidal side effects cause depolarization block of the motor-related substantia nigra cells. [p. 117]

Even reviews that suggest an etiological role in schizophrenia of other areas (e.g., the frontal cortex; Pettegrew and Minshew 1992) refer to the mesolimbic system in explaining antipsychotic drug action. Indeed, investigations that are clearly directed toward assessment of pharmacological specificity rather than anatomical selectivity eventually look to the mesolimbic system for validation. For example, Crawley (1991) asserts that the modulatory influences of cholecystokinin (CCK) on DA are worthy of investigation, in part because of their localized effect. "The circumscribed anatomical distribution of CCK within the larger dopaminergic system raises the attractive possibility that CCK-based drugs could provide more anatomically specific therapeutic approaches for disorders linked to the mesolimbic..."

To what can the strong belief in the primacy of the mesolimbic system be attributed? Initially, the mesolimbic theory provided the rationale for developing a “magic bullet” to treat schizophrenia; a drug with mesolimbic-specific activity would alleviate the symptoms of schizophrenia without the motor side effects of conventional neuroleptics (e.g., Crawley 1991; Bjork et al. 1992; Christensson 1992; Skarsfeldt 1992). However, despite the fact that current research is directed more toward pharmacological specificity than toward anatomical localization, the idea persists. Perhaps this longevity is due to the very considerable heuristic strength of the mesolimbic hypothesis. Assumptions based on it seem to explain the unique symptoms of schizophrenia without the motor side effects of conventional neuroleptics (e.g., Crawley 1991; Matthysse 1973; Stevens 1972; Anden et al.’s 1966 discovery that DA was also present in areas intimately associated with the limbic system provided conceptual relief (Anden 1972; Matthyssse 1973; Stevens 1973).

While little was known then of the behavioral functions of the nuclei of the mesolimbic DA system, much work had been done on the brain areas with which these nuclei are interconnected. Limbic system structures are heavily implicated in the control of affective, attentional, and mnemonic processes. A pivotal article in the evolution of the mesolimbic theory of schizophrenia (Stevens 1973) emphasized the similarities in symptoms between cases of epilepsy involving limbic nuclei and persons with schizophrenia. In calling particular attention to disturbances of emotion, attention, and memory in both types of disorders, Stevens gave credence to the idea that mesolimbic disturbance led to schizophrenia. She asserted that if drugs could be specifically targeted for action in the mesolimbic system, alleviation of schizophrenic symptoms could be achieved while reducing “the incidence of side effects due to simultaneous effect on neostriatal structures” (p. 187).

Although many have so suggested, it is not necessary to hypothesize that mesolimbic dysfunction per se is etiological for schizophrenia. Pathological functioning in a different area that is afferent to the mesolimbic nuclei could be offset by corrective pharmacological activity in the mesolimbic nuclei. For example, Jaskiw and Weinberger (1992) point out that while the most convincing evidence for a structural and functional defect in the schizophrenic brain focuses on the frontal cortex, it is plausible that corrective action can be accomplished via pharmacological influences on the targets of prefrontal output. Among these targets is the mesolimbic DA system.

Thus, at its inception, the mesolimbic theory was based on two key assumptions. First, the symptoms of schizophrenia reflect disturbances of behaviors that are mediated and/or influenced by the mesolimbic DA system. Second, the functions of the nigrostriatal DA system are primarily motoric and are therefore not involved in schizophrenia to an important extent. Considering the information available in the early 1970s, these assumptions appeared entirely reasonable. However, considerable new data have been amassed that reflect on the validity of these suppositions and the theory to which they are integral. A reevaluation would be timely and is the purpose of the present article.

Do the Symptoms of Schizophrenia Reflect, in Large Part, Disturbances of Behavioral Functions That Are Mediated or Influenced by the Mesolimbic DA System? The behavioral functions of the mesolimbic DA system are still largely unknown. In contrast, the actions of the main source of afferents into the mesolimbic nuclei (i.e., the limbic system) are clearly crucial to normal affect, memory,
and attention (e.g., LeDoux 1987). As stressed by Stevens (1973), dysfunctions involving these behavioral processes are among the most prominent symptoms of schizophrenia. But the question remains: Is the mesolimbic system itself involved in these functions? Little work has been done that directly reflects on the possible role of the mesolimbic system in either memory or attention. Certainly, the finding that addictive drugs have potent effects on mesolimbic structures (Di Chiara et al. 1987; Wise and Bozarth 1987) is suggestive of involvement in motivational aspects of behavior. However, it must also be recognized that such effects are not confined to the mesolimbic component of the ascending DA systems (Izenwasser et al. 1990; Robinson and Camp 1990). Similarly, Ljungberg et al. (1992) has found that dopaminergic neurons in the ventromedial tegmentum, the source of DA in mesolimbic structures, respond to reward as well as to stimuli that predict reward. Dopaminergic neurons in the substantia nigra behave similarly (Ljungberg et al. 1992). Perhaps the summary statements of a recent review of mesolimbic functioning best summarize the continuing uncertainty:

It seems very possible that activation of this circuitry by positive reinforcing environmental stimuli ... might contribute to motivated behavior ... It is also tempting to speculate that pathological changes in activity within this system might disrupt normal reinforcement contingencies, and contribute to the affective components of both psychiatric and neurological disease states. [Koob and Swerdlow 1988, p. 225]

Thus, the assumption regarding similarity of behavioral functions affected by schizophrenia and those mediated by the mesolimbic system is “tempting” but, as in 1973, remains speculative.

**Do the Symptoms of Schizophrenia Not Reflect Disturbances of Functions Mediated by Striatal Components of the Ascending DA Systems?** When the mesolimbic theory was originally suggested, the striatum was thought to function primarily in motor control. Since schizophrenia was viewed as a mental illness, processes integral to this disease were considered beyond the functioning of the basal ganglia. However, Kraepelin’s (1919/1921) original descriptions of schizophrenia pointed out that motor symptoms were frequently associated with schizophrenia. Mettler (1955) also described similarities between some of the movements he observed in institutionalized schizophrenia patients who had never been exposed to neuroleptics and those seen in patients with extrapyramidal disorders. More recently, several investigators (reviewed in Manschreck 1986) have noted a variety of abnormal movement patterns in schizophrenia patients and have suggested that these symptoms reflect the disease rather than the effects of neuroleptic drugs. In addition, Holzman and colleagues (e.g., Holzman et al. 1977) have described abnormal eye tracking movements in both schizophrenic persons and their close relatives.

These motor signs are of minor clinical significance compared with the impact of the affective, attentional, and mnemonic disturbances of schizophrenia. In contrast, their theoretical significance may be considerable. The existence of motor symptoms, particularly those that are “extrapyramidal” in form, indicates that the pathophysiological disturbance in schizophrenia may involve the striatum. Indeed, observations of this type led earlier investigators to posit basal ganglia dysfunction in schizophrenia (Mettler 1955). Although certainly not a primary focus in schizophrenia research, evidence of such dysfunction persists even with modern imaging techniques (e.g., Buchanan et al. 1993). This in itself would be of little import if the earlier conceptualizations of basal ganglia functioning were accurate. However, it is now clear that basal ganglia activities are not limited to the sphere of movement control.

The striatum, in primates, is composed of the putamen and the caudate nucleus. Although they are similar in morphology and histocomposition, the anatomical connections of the caudate and putamen differ. The putamen receives a strong projection from the primary somatosensory and motor cortices. Putamen influences, via the pallidothalamic connections, are exerted on the supplementary motor area. This pathway is taken to represent the basal ganglia’s “motor loop” and to mediate this system’s role in the control of movement (Evarts et al. 1984). In contrast, the caudate nucleus receives fibers from frontal association cortices and is thought to participate in “complex” functions (Evarts et al. 1984). It is relevant, in the present context, that among the complex behavioral activities mediated by this portion of the basal ganglia are mnemonic (Wyers et al. 1968; Stamm 1969; Cohen 1972) and cognitive (Bowen 1976; Lidsky et al. 1985; LaPlane 1990) processes. Memory disturbance, as noted by Stevens (1973) in support of the mesolimbic hy-
pothesis, is an important component of schizophrenia. It is ironic that memory functions, although attributed to the mesolimbic system by theory, can be ascribed to the striatum via empirical evidence.

The striatum’s role in cognitive processing raises another issue. The mesolimbic theory, as originally promulgated (Stevens 1973), stresses the affective, attentional, and mnemonic components of schizophrenia. However, profound cognitive disturbances are also seen in this disease (Gur et al. 1991). Clearly, there is no a priori reason based on clinical findings, anatomical connections, or experimental work in laboratory animals to attribute a role in cognition to the mesolimbic system. It is possible that the mesolimbic system has an indirect role in cognition via influences of the nucleus accumbens on the nucleus basalis (Richardson and DeLong 1988). The latter structure, primarily because of its putative role in Alzheimer’s disease, is thought by some to be important in cognition. However, the function of the nucleus basalis in Alzheimer’s disease is by no means clear (e.g., Nakano and Hirano 1983; Pearson et al. 1983). Moreover, the nucleus accumbens is not unique as a source of afferents; the striatum also projects to the nucleus basalis (Richardson and DeLong 1988).

In contrast, data from work in humans and in experimental animals suggest an important role of the striatum in cognitive processing (Bowen 1976; Lidsky et al. 1985; LaPlane 1990; Schneider and Kovelowski 1990). The consistent findings in studies of the schizophrenic brain of abnormalities in structure, pharmacology, and function of the prefrontal cortex (Jas-kiw and Weinberger 1992) may be relevant in this context. Prefrontal association areas are thought to serve a primary role in cognitive activities and are also the major source of cortical afferents to the caudate nucleus (Evarts et al. 1984).

The striatum’s role in complex behaviors may not be limited to memory and cognition. As previously noted, DA neurons in both the ventromedial tegmentum and the substantia nigra are similarly activated by reward and stimuli that predict reward (Ljungberg et al. 1992). Clinical data indicate profound changes in affect following small lesions in the lenticular nuclei (putamen and globus pallidus) (LaPlane 1990). Patients with this damage showed loss of drive and a dramatic flattening of affect. Emotions, although not always absent, were exceedingly short-lived and changed in character. Emotional states “seemed more intellectual than truly affective” (LaPlane 1990, p. 30). These changes were seen in patients with and without concomitant motor signs. Thus, the mesolimbic system may not be unique among components of the DA system in playing some role in affect.

Similarly, some of the motor functions ascribed to the striatum may also reside in the mesolimbic system. Anatomists have remarked that “much of the output of the ventral striato-pallidal system is directed toward motor targets” (Heimer et al. 1982, p. 83). Studies of the effects on sexual behavior of apomorphine injections into the ventral tegmental area indicated a role in motor or sensorimotor aspects of copulation rather than in sexual motivation (Hull et al. 1991). The amygdala, a major source of afferents into the nucleus accumbens, has a strong modulatory influence on trigeminal reflexes involving jaw movements (Gary-Bobo and Bonvallet 1975; Sessle 1977). It may therefore be no coincidence that ventral pallidal neurons show activity related to sensorimotor aspects of chewing (DeLong 1971). It seems plausible that dysfunction in this part of the mesolimbic system could produce some of the symptoms associated with tardive dyskinesia.

Two final points should be noted regarding the distribution of DA. First, recent investigations using highly sensitive assays have revealed that dopaminergic innervation is even more widespread than previously believed. In addition to the DA in the nigrostriatal, mesolimbic, and mesocortical projections, it is now recognized that virtually all areas of the cortex (Richfield et al. 1990), as well as traditional limbic structures such as the hippocampus (Bischoff 1992), have significant DA activity.

The cortical and limbic dopaminergic populations take on added significance with respect to the new generation of atypical antipsychotic drugs. As Seeman (1992b) points out, the high dissociation constants at D2 receptors that characterize many of these agents would make their binding highly sensitive to the local concentration of DA. Because of competitive antagonism, atypical neuroleptics “would occupy more dopamine receptors in brain regions having low dopamine output ... but would occupy fewer dopamine receptors in regions having high dopamine output ...” (Seeman 1992b, p. 147). Thus, atypical antipsychotics would affect traditional limbic structures and the cortex at lower dose levels than would be required to affect the mesolimbic
nuclei and basal ganglia. Inasmuch as the limbic system and cortex cover the gamut of behavioral functions, it seems even more unlikely that only mesolimbic DA activity is critical with regard to antipsychotic drug action (e.g., Lewis et al. 1992).

Second, molecular cloning studies have determined that there are at least three additional types of DA receptors (D_3, D_4, D_5) (Sibley and Monsma 1992; O'Dowd 1993). The D_4 receptor is particularly relevant to the arguments put forth in the present article. The affinity of clozapine for the D_4 receptor is 10 times greater than for either the D_2 or D_3 receptors. Moreover, the therapeutic concentration of clozapine in patients' plasma water or cerebrospinal fluid correlates with action at the D_4 receptor (Seeman 1992a). In the human, D_4 mRNA is localized much like D_2 mRNA, with significant distributions in the caudate, putamen, and substantia nigra (O'Dowd 1993).

Thus, clozapine's antipsychotic efficacy may include action in the basal ganglia. This may also be true of conventional neuroleptics. Buchsbaum and coworkers have suggested that a favorable clinical response to haloperidol is predicted by the predrug metabolic rate in the striatum (Buchsbaum et al. 1992). Attempts to confirm these results with different patient populations and other conventional neuroleptics are needed.

Investigations of clozapine's non-dopaminergic mechanisms of action also shift the focus away from the mesolimbic DA system. Meltzer has suggested that clozapine's action at the serotonin (5HT_2) receptor contributes significantly to this drug's antipsychotic potency (Meltzer 1991). Meltzer's suggestion that cortical receptors would be important in this regard has been borne out by positron emission tomography in psychiatric patients (Nordstrom et al. 1993). However, affinity for the 5HT_2 receptor alone does not determine the unique properties of clozapine, since similarly high affinities are demonstrated by typical neuroleptics such as chlorpromazine, fluphenazine, and trifluoperazine (Meltzer et al. 1989). Moreover, addition of a serotoninergic blocker to the archetypal conventional neuroleptic haloperidol does not imbue this antipsychotic with the atypical properties of clozapine (Lappalainen et al. 1990). Meltzer has argued that, while affinity for 5HT_2 receptors per se does not presage clinical effects similar to those of clozapine, the ratio between 5HT_2 and D_2 pKi's (negative log of the affinities) is predictive (Meltzer et al. 1989; Meltzer 1991).

Conclusions

The mesolimbic hypothesis of antipsychotic actions was based on inaccurate assumptions about the behavioral functions of the different components of the ascending DA systems. Affect, memory, and cognition, thought to be mediated primarily by the mesolimbic system, are also within the province of striatal processing. Conversely, the mesolimbic system probably plays some role in motor control. In addition, significant DA activity is found in a variety of cortical and subcortical areas outside the traditional mesolimbic, nigrostriatal, and mesocortical DA systems. Thus, while action in the mesolimbic DA system may be necessary for antipsychotic effects, such action in isolation is probably not sufficient. It is clear, however, that a drug with strong antipsychotic potency and a reduced risk of motor side effects is possible. The success of clozapine demonstrates this point unequivocally (Safferman et al. 1991). It is significant in the context of the present discussion that the unusual clinical profile of clozapine, although originally attributed to mesolimbic-specific action (e.g., Anden and Stock 1973), is currently thought to reflect the unique pharmacological properties of this drug (Meltzer 1991; Lidsky and Banerjee 1992; Seeman 1992a, 1992b; Lidsky et al. 1993).

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Announcement

The Theodore and Vada Stanley Foundation, in collaboration with the National Alliance for the Mentally Ill, welcomes applications for the 1995 Stanley Foundation Research Awards Program. The purpose of the awards is to support research directly related to the causes and treatment of schizophrenia, bipolar disorder, and major depression. The research awards are intended to attract established scientists from other areas of biology and medicine (e.g., biochemistry and neurology) into research on serious mental illnesses, as well as to provide support for innovative research by scientists already in the field whose funding sources are limited. Awards are for 1 or 2 years and may be up to $50,000 per year for nonhuman research and up to $75,000 per year for research that includes human subjects. In 1994 a total of 52 awards were funded out of 223 applications.

Applications must be submitted by March 1, 1995 (1 month earlier than last year). Notification of awards will be made in June and funding will begin in August. Application forms consist of a brief outline of the proposed project, a budget, and a list of current and pending sources of funding. Funds may be used for salaries, supplies, and equipment, but it is the policy of the Stanley Foundation not to pay indirect costs. The research award applications are reviewed by a professional selection committee. Requests for applications and questions should be directed to:

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