A Strategy for Developing Novel Drugs for the Treatment of Schizophrenia

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Abstract

Antipsychotic drugs currently in use have been developed as antidopaminergic agents; that is, normalization of psychotic symptoms occurs through a reduction in dopaminergic activity, usually by blockade of postsynaptic dopamine receptors. Based on this current understanding of the mechanism of action of antipsychotic drugs, it is suggested that one physiological role of the dopaminergic system is to downregulate in the face of biological or psychological insult, as a means of maintaining mental stability. An attempt to develop new drugs to improve the efficiency of this downregulative system as an alternative to conventional drugs that block dopamine receptors is proposed.

Schizophrenia is a disorder whose etiology is unknown, whose boundaries are unclear, whose pathophysiology is undiscovered, and whose course is highly variable. Since the serendipitous discovery that antidopaminergic drugs could relieve some of the symptoms of schizophrenia some of the time, the development of new classes of drugs for the treatment of this disorder has generally followed two approaches. The first approach involves the synthesis of compounds that are structurally similar to existing antipsychotic drugs in the hope that they will have a more favorable profile; the second approach involves the development of novel structures that, nonetheless, retain the antidopaminergic properties of conventional neuroleptics. Both of these approaches produce so-called "me too" drugs whose properties tend to differ from established compounds mainly in potency and side effect profile. Must we then give up hope for the development of genuinely novel treatment approaches until we understand the etiology and pathogenesis of schizophrenia, or can we devise new treatment modalities based on existing knowledge?

What Is It That We Are Trying to Treat?

Schizophrenia, for all of its profound and often catastrophic effects on the social function of its victims, is a mild disease in the physiological sense. None of the multiple laboratory probes of human function, so successful in detecting other disorders, have ever been found to be consistently abnormal in schizophrenic patients. In the absence of its mental and characterological manifestations, schizophrenia would be undetectable by any means known today. Although the term "symptomatic treatment" is usually used in a pejorative sense to designate a treatment that is only palliative, in schizophrenia, a drug that could successfully block symptoms, without significant side effects, would leave no known residues. Thus, it should be clear that what we are trying to treat, considering our present state of knowledge, is the symptomatology of schizophrenia. Development of a universally effective symptomatic treatment would represent an important advance, and would be more than mental aspirin.

Modern History of Development of Antischizophrenic Drugs

Drug development, based on theories about the etiology of schizophrenia,
has been attempted. One such approach was based on the observation that methoxylated phenethylamines such as mescaline could produce some of the symptoms of psychosis. This led to intensive investigation of the role of excessive or aberrant methylation in the pathogenesis of schizophrenia (Osmond and Smythies 1952; Pollin, Cardon, and Kety 1961; Friedhoff and Van Winkle 1964; Rosengarten and Friedhoff 1976) in the hope that drugs could be developed that would interfere with the formation of psychototoxic substances. Although the methyl donor, methionine, was observed to exacerbate symptoms, presumably because it increased toxic methylation (Pollin, Cardon, and Kety 1961), the methyl group acceptor, nicotinic acid, did not prove to be an efficacious treatment (Ramsay et al. 1970); however, the hypothesis may not have been adequately tested by use of this substance because it has not been demonstrated to diminish ongoing methylation of other substances in vivo. Theory-derived drug development has not yet provided effective pharmacotherapy for schizophrenia, but the potential has not been exhausted. For example, no potent O-methyltransferase inhibitors have been subjected to clinical trial.

After reserpine and later chlorpromazine, both of which were under study for other purposes, were found to have antipsychotic activity, there was intense interest in understanding their mechanism of action. It was found that both classes of drugs had the ability to reduce dopaminergic activity, although by different mechanisms (Anden, Roos, and Wedinus 1964). Carlsson’s classic studies, showing that phenothiazines acted as dopamine receptor blockers (Carlsson and Lindqvist 1963), provided the impetus for the development of the dopamine hypothesis of schizophrenia (Friedhoff and Van Winkle 1964; van Rossum 1967). This hypothesis stated that the schizophrenic syndrome was caused by hyperdopaminergia—loosely referring to increased output of the dopaminergic system. The rationale for this hypothesis was that if the symptoms of schizophrenia were relieved by a reduction in activity of the dopaminergic system, then schizophrenia itself must involve overactivity of that system.

In retrospect, this hypothesis, although disarmingly straightforward, was based on less than steel-trap logic. Perhaps the most compelling single argument against the dopamine hypothesis as it was originally formulated is the fact that antipsychotic drugs are not disease specific. These drugs are active against symptoms of organic psychosis, amphetamine psychosis, manic-depressive psychosis, schizophrenia, other functional psychoses, and the nonpsychotic illness Tourette syndrome. Thus, the argument that hyperdopaminergia is the cause of schizophrenia could be equally applied to other syndromes that are responsive to neuroleptic treatment. Therefore, either dopamine is involved in the pathophysiology of symptoms that are common to all of these illnesses, or it is involved in other mechanisms common to them all. At the very least, the hypothesis should be renamed the “dopamine hypothesis of psychosis.” Even this broadened concept, however, has been undermined by the failure, thus far, to find either physiological or metabolic evidence of hyperdopaminergia as a common denominator of at least a subtype of schizophrenia. Despite the large number of investigations into this subject, no credible reports of increased turnover of dopamine in schizophrenics can be found in the literature. The failure to find this evidence has shifted interest to the study of dopamine receptors. The study of the status of brain membrane receptors in living humans presents an unusual challenge, inasmuch as no known peripheral marker of central dopamine receptor status has been discovered.

Although the dopamine hypothesis, as originally proposed, has serious weaknesses, it has not yet reached the point in Kuhnian terms (Kuhn 1962) where it is ready to be overthrown and replaced by another. This faulty proposal remains viable for two important reasons: (1) dopamine receptor blockers do produce significant therapeutic effects in many patients with psychosis; and (2) no viable alternative to this hypothesis has been presented. Is there, however, a possible reformulation of the dopamine hypothesis that could serve as a basis for development of new drugs?

Restitutive Systems in the Brain

After it was observed that neuroleptics could produce a Parkinsonian-like extrapyramidal syndrome, Haase and Janssen (1965) reported that those patients who developed this syndrome responded better to neuroleptic treatment. This assumption seemed logical inasmuch as the drugs were believed to act through their ability to block dopamine receptors and the extrapyramidal syndrome occurred as a result of effective blockade in the striatum. Other studies, however, did not support this finding (Karn and Kaspr 1959; Hollister, Chaffey, and Klette 1960; Goldman 1961; Simpson et al. 1964), and ultimately the hypothesis was abandoned.

With the shift in interest from metabolism to receptors, and the
development of appropriate methodology, the adaptive nature of the dopaminergic system came under intensive investigation (Burt, Creese, and Snyder 1976; Muller and Seeman 1976; Friedhoff 1977; Friedhoff and Alpert 1978). It is now well established that the number of specific dopamine sites adapts to the available supply of dopamine. For instance, when dopaminergic activity is decreased through the action of dopamine receptor blockers, a relatively persistent compensatory increase in the number of dopamine receptor binding sites occurs; this compensatory increase results in supersensitivities of the system, which may not be detectable until after drug discontinuation and elimination of further receptor blockade (Seeman 1980). The compensatory response of the dopaminergic system has been hypothesized to play a role in the pathophysiology of tardive dyskinesia (Fann et al. 1980).

Decreases in the concentrations of dopamine impinging on dopamine receptor sites as a result of neuroleptic blockade, depletion of dopamine by reserpine or through section of the nigrostriatal dopaminergic tract all result in a compensatory increase in the number of postsynaptic receptors. When dopamine receptor blocking neuroleptics are administered, the initial response in some brain areas, like the striatum, is an increased release of dopamine from the presynaptic terminal (Carlsson and Lindqvist 1963; Miller and Friedhoff 1978). If the blockade is incomplete, presumably the additional release can compensate for the drug-induced blockade of dopaminergic activity and reestablish the original homeostatic relationships. If the blockade is more complete, then the initial release is later followed by an increase in the number of dopamine receptor binding sites (Seeman 1980). The appearance of additional sites moves the system toward the reestablishment of the level of dopaminergic activity that existed before the administration of neuroleptic. If neuroleptic concentrations are high enough, the new dopamine sites will also be blocked and the compensatory attempt will be unsuccessful. If drug is subsequently withdrawn, however, the blockade will be terminated and the presence of an excess number of receptor sites will make the system supersensitive to dopamine. This state of supersensitivity is associated with drug withdrawal dyskinesia. The dopaminergic system can sometimes become functionally supersensitive, even in the continued presence of neuroleptic (Clow et al. 1979), and this phenomenon is believed to be associated with tardive dyskinesia.

Compensatory changes have also been described in the β-noradrenergic system. It is well established that the increased release of norepinephrine, such as is produced by antidepressant drugs, later results in a reduction in the density of β-noradrenergic sites (Vetulani et al. 1976; Sulzer, Vetulani, and Mobeley 1978). Also, it has been found by Stone (1979) that rats subjected to certain types of prolonged stress, after an initial surge in noradrenergic activity, have a persistent reduction in the activity of the noradrenergic system. Rats exposed to one stress become resistant to both the biological and behavioral effects of a subsequent stress. Antidepressant drugs mimic the effects of stress because they increase the resistance of the rat to the effects of stress, and bolster the efficiency of physiological stress resistance mechanisms in the brain. Although the mechanism by which antidepressants achieve this effect is not entirely understood, it is believed that their mechanism of action involves a compensatory decrease in the number of β-noradrenergic receptors. This down-regulation is a secondary response to the increased concentration of norepinephrine at the synapse, which is the initial effect of antidepressant treatment. Thus, the down-regulation represents a compensatory response which moves the system toward the reestablishment of the initial level of noradrenergic activity.

The regulatory systems controlling the number of postsynaptic receptors in both the β-noradrenergic and the dopaminergic systems are responsive to perturbations that affect the level of activity in the system. As has been shown above, each system responds by attempting to reestablish the level of activity that existed before the perturbation. Drugs that block access of the transmitter to the postsynaptic receptors will produce a compensatory increase in the number of those receptors while drugs or other factors that increase transmitter release will produce a secondary down-regulation by means of a complex system designed to maintain functional stability and integrity.

It seems unlikely that this marvelous plasticity serves only to mediate drug effects. More likely, the compensatory capability of the biogenic amine systems is important in the regulation of physiological functions. We can get a clue to the nature of the physiological role of these systems from the kinds of drug effects that they mediate. Neuroleptic drugs that suppress psychotic symptoms do so, at least in part, by diminishing dopaminergic activity. It seems plausible, therefore, to assume that the dopaminergic system is involved in protecting against the emergence of such symptoms through physiological down-regulation in the face of psychological or biological
events that would tend to destabilize the system. In this context, the dopaminergic system may maintain mental equilibrium by spontaneous down-regulation of its own function, when this is necessary to prevent disturbances in the dynamic equilibrium of central nervous system function. The dopaminergic system can be viewed as a restitutive or buffer system following the classical denervation supersensitivity model of Cannon and Rosenbleuth (1949). Although the system adjusts itself in such a way as to restore its own homeostasis, this adjustment very likely also affects other brain systems, inasmuch as the brain functions in a dynamic fashion, so that a change in one functional aspect produces a series of changes in other functional units (Bernard 1957; von Bertalanffy 1969).

Experimental Evidence Supporting the Restitutive Hypothesis

The level of activity in the dopaminergic system is a function of many factors. Two important determinants of this level are the rate of release of dopamine into the synapse, and the number of postsynaptic receptors available to dopamine. There is presently no satisfactory measure of brain dopamine release or turnover in humans; however, an approximation can be made by the measurement of dopamine metabolites in spinal fluid. Neuroleptic blockade of dopamine receptors provokes a compensatory release of dopamine which can be detected by an increase in dopamine metabolites in spinal fluid. Chase, Schnur, and Gordon (1970) have found that the less dopamine released in response to neuroleptic treatment, the greater the neuroleptic-induced extrapyramidal syndrome. The dopamine released into the synapse tends to overcome the neuroleptic blockade; thus the less the release, the more effective the blockade. Crowley et al. (1976) have found a similar relationship by measuring dopamine metabolites in urine, although this measure probably reflects primarily dopamine metabolites of peripheral origin.

Based on these observations, Alpert, Diamond, and Kesselman (1977) and Gutierrez et al. (1979) devised a test of the functional level of the dopaminergic system in humans. By administering a standard dose of neuroleptic for a short period and measuring the resultant rigidity and tremor, they estimated the functional level of the striatal dopaminergic system. Using this technique, they found that patients with the most drug-induced extrapyramidal effects had the poorest therapeutic response to continued drug treatment; that is, those patients with low preexisting dopaminergic activity did not get a good response to neuroleptics. Inasmuch as the object of neuroleptic treatment is to reduce dopaminergic activity through receptor blockade, it seems paradoxical that those individuals with low preexisting dopaminergic activity had the poorest response to treatment.

A compelling interpretation of these findings is that factors that tend to destabilize mental function produce a compensatory down-regulating response in the dopaminergic system. In some individuals, this response is adequate to maintain stability and no psychotic symptoms appear. In others, the destabilizing factors are so severe that maximal down-regulation cannot stave off psychosis. These subjects will have low pretreatment levels of dopaminergic activity reflected by sensitivity to the extrapyramidal effects of neuroleptics. A further decrease in dopaminergic activity cannot be achieved with neuroleptic treatment in these subjects because of the low pretreatment level. Thus, neuroleptics will be ineffective, and the subjects will be considered to be treatment resistant. On the other hand, in those individuals with symptoms in whom the dopaminergic system has not reached bottom through inadequate ability of this system to tune itself down, the administration of neuroleptic drugs can further reduce dopaminergic activity and induce a remission in symptoms.

It is not clear why all schizophrenic patients do not reduce their own dopaminergic activity maximally without neuroleptic treatment. It has been shown that prenatal influences can dramatically alter the postnatal plasticity of the striatal dopaminergic system (Rosenzweig, Friedhoff 1979, unpublished data). Undoubtedly, other developmental and genetic factors also affect the capacity and responsivity of this adaptive mechanism.

The dopaminergic system appears to be one of a number of central restitutive systems whose function is to maintain mental stability. Dopamine does not seem to be involved as a primary etiological factor in the psychotic process; that is, it is not necessary to be hyperdopaminergic to have psychotic symptoms, but when appropriate etiological and precipitating factors exist, a significant decrease in the activity of the dopaminergic system may stave off mental breakdown.

Deficit Symptoms and the Restitutive System

From a broad range of clinical experience, it is known that the so-called "deficit" symptoms of
schizophrenia respond poorly to neuroleptic treatment. Patients showing primarily deficit symptoms may actually get worse after neuroleptics. Deficit symptoms include flat affect, emotional withdrawal, the amotivational-anhedonic state, poor social interaction, and, by extension, poor premorbid adjustment. Flat affect, a primary deficit symptom, may itself be a manifestation of the dopaminergic compensatory system in action; that is, flat affect may occur as a manifestation of a spontaneous compensatory reduction in the activity of the dopaminergic system. This is supported by the observations made by Alpert and Rush (1983) that patients with naturally occurring Parkinson's disease (associated with low dopaminergic activity) manifest a flatness of expression that is difficult to differentiate from flat affect in schizophrenia. Additionally, neuroleptics, presumably through their dopamine receptor blocking action, often produce a notable affectual blunting. Thus, flat affect appears to be associated with low dopaminergic activity (Alpert and Rush 1983) and is a prominent symptom in poor prognosis schizophrenics (Alpert and Friedhoff 1980). This is further support for the proposal that those patients with a hypoactive dopaminergic system can get little by way of further down-regulation from neuroleptics and are therefore resistant to treatment with these agents.

The dopaminergic system can thus be viewed as a system for maintaining homeostatic relationships in the presence of biological or psychological insult. A reduction in dopaminergic activity enhances mental stability in the face of unknown precipitating or etiological factors. From this standpoint, mental breakdown occurs when the etiological factors are so potent as to overwhelm the restitutive system.

Treatment-resistant patients can be thought of as those whose dopaminergic activity has been spontaneously reduced to the lowest possible level without a resultant remission in symptoms. In treatment-resistant patients, because of the potency of the precipitating factors, or because of an innate inadequacy of the restitutive mechanism, a maximal level of compensation has failed to prevent the emergence of the psychosis. Thus, the specific problem in some patients with schizophrenia or other psychoses could be a polygenically or developmentally determined defect in the function of a dopamine dependent restitutive system. In that case, treatment to increase the efficiency of the system, by forcing a reduction in dopaminergic activity, when that is possible, can be viewed as both a specific and a symptomatic treatment.

How Can This Model Be Used to Develop Novel Drugs?

Based on the evidence presented, it appears that an important mode for physiological regulation of dopaminergic activity occurs through an adaptive decrease in activity of the dopaminergic system. Antipsychotic drugs currently in use have been designed to produce an acute decrease through blockade of receptors. This results in a compensatory increase in the number of dopamine sites, perhaps offsetting the benefits accruing from the blockade, and increasing the risk of tardive dyskinesia. One approach to new drug development should involve the design of compounds specifically tailored to decrease dopaminergic activity by direct down-regulation of the dopaminergic system without a subsequent compensatory up-regulation. Although the molecular mechanisms involved in up- and down-regulation of receptors are not clear, it is possible to modify the number of dopamine binding sites by manipulation of dopamine release.

The technique of receptor sensitivity modification (RSM) has provided the basis for a novel therapeutic approach. This approach was developed as a treatment for conditions believed to be responsive to a reduction in dopaminergic activity, e.g., tardive dyskinesia, schizophrenia, and Gilles de la Tourette syndrome (Friedhoff 1977; Friedhoff and Alpert 1978). RSM involves the production of increased dopaminergic activity by the administration of a dopaminergic agonist or agonist precursor, which, in turn, produces a secondary down-regulation of dopamine receptors. A net reduction in dopaminergic activity is achieved when the agonist or precursor is withdrawn. In RSM, L-dopa is administered over a period of weeks, in gradually increasing doses. Inasmuch as L-dopa is the immediate precursor of dopamine, treatment with L-dopa increases the biosynthesis and release of dopamine in the brain. This approach is being used for conditions in which hyperdopaminergia appears to be a problem, so that the initial increase in dopaminergic function tends to worsen the symptoms; however, chronic administration of L-dopa has been shown to reduce the number of dopamine receptors (Friedhoff, Bonnet, and Rosengarten 1977). Thus, when L-dopa treatment is discontinued, symptom reduction based on reduced dopaminergic function is anticipated.

To date, the RSM approach has produced promising results. Alpert, Friedhoff, and Diamond (1983) carried out a study in which gradually increasing doses of L-dopa plus carbidopa (sinemet) were given
to 15 subjects with severe tardive dyskinesia. All were continued on either their normal neuroleptic treatment or no treatment except the sinemet. A comparison group of 10 equally affected patients were treated as before the study without the addition of sinemet. About 50 percent of the sinemet-treated patients showed clinically significant improvement 4 weeks after termination of sinemet. The comparison group showed no significant change in level of symptoms. There are disadvantages to this approach. Because the induction of down-regulation requires initial overstimulation, patients usually get somewhat worse before they get better. Also, the down-regulation induction with a dopaminergic agonist takes from 1 to 2 months.

New drugs designed specifically to produce enduring down-regulation should be capable of inducing and maintaining an adaptive down-regulation response without worsening the subject. These conditions cannot be met by the use of currently available dopaminergic agonists. Recent research has provided some leads that may permit the induction of down-regulation without the necessity for overstimulation of postsynaptic cells. Roberts and Bloom (1981), in a seminal experiment, provided evidence that a cell can regulate the number of its own membrane receptors. A better understanding of this regulatory system may provide pharmacological access routes that eliminate the necessity for overstimulation of the cell as a means of down-regulation. In order to capitalize on these leads, it is necessary to begin to assess further the physiological role of the adaptive aspect of the dopaminergic system, and of other systems with which it is interactive. Almost invariably this will lead to the development of compounds that will initiate these adaptive responses and provide a workable strategy for new drug development.

To develop drugs of this type, it will be necessary to determine at what loci the regulatory system of the receptor can be intercepted without generating a compensatory overriding reaction. The receptor is a complex unit involving recognition, coupling, and response elements, and each of these loci is capable of influencing the responsivity of the system. For instance, the mechanism coupling the receptor recognition site to the response mechanism is a possible site of pharmacological intervention. More fundamental regulatory sites might also be altered pharmacologically as in the study of Roberts and Bloom (1981), in which adrenal steroids were shown to affect receptor adaptation.

These exciting prospects are all contingent on the development of additional insights into the adaptive nature of the biogenic amine systems. These insights may make it possible to design new kinds of pharmacological treatments and to improve understanding of the pathophysiology of the serious mental disorders. Most important, perhaps, further knowledge about these adaptive systems may make it possible to understand the mechanisms involved in the maintenance of relative mental equilibrium.

References


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- A book or paper, or a group of representative, and thematically linked, books or papers published (or accepted for publication) in English and dated within 10 years before the deadline of submission.
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