Dopamine Receptor Supersensitivity and Schizophrenia: A Review

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Abstract

Advances in knowledge of brain neurochemistry have lent impetus to the biological study of schizophrenia. A prominent example is the dopamine hypothesis. Increasing additions to and refinements of neurochemical knowledge, particularly the study of receptors, have continued to support biological hypotheses of schizophrenia. A recently proposed hypothesis is that schizophrenic patients suffer from dopamine receptor supersensitivity at certain phases of their illness. The present article selectively reviews data that are relevant to this refinement of the dopamine hypothesis.

The dopamine hypothesis is widely held as a possible biological basis for schizophrenia. Most succinctly, this hypothesis states that schizophrenia may be related to a relative excess of dopamine (DA) mediated neuronal activity. Drugs that block postsynaptic DA activity (e.g., the phenothiazines) can be antipsychotic, and drugs that increase DA synaptic activity (e.g., amphetamines) can be psychotomimetic (Carlsson and Lindqvist 1963; Snyder et al. 1974; Meltzer and Stahl 1976; Bunney et al. 1979). Evidence consistent with the hypothesis still has not been transformed into etiological principles of a theoretical framework within which most clinical, as well as biochemical, data would easily fit.

Specifically, several pertinent clinical facts must be considered:

- Schizophrenia is a syndrome. The current approaches to diagnosis, such as the Feighner Criteria (Feighner et al. 1972), the Research Diagnostic Criteria (Spitzer, Endicott, and Robins 1975), the International Pilot Study of Schizophrenia Criteria (Carpenter, Strauss, and Bartko 1973), the New Haven Schizophrenia Index (Astrachan et al. 1972), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association 1980) attempt to define a group of patients on the basis of objective symptomatic manifestations. Thus, the current approach to categorization yields a syndrome (viz., Gk., running together) not a specific disorder—a pathological entity more similar to a condition (e.g., general congestive heart failure) than to a specific disease with known structure and etiology (e.g., congestive heart failure as a syndrome resulting from Rocky Mountain spotted fever).

- The course of the illness shows variable symptomaticity within an individual. More specifically, psychotic disorganization appears to be only one phase—albeit the phase from which the diagnosis is often made—in the course of a more pervasive and longitudinal disorder.

- Phenothiazines are better considered antipsychotic than anti-schizophrenic. They are anti-schizophrenic only to the extent that they ameliorate and prevent recurrence of psychotic symptoms. Phenothiazines are efficacious for psychotic symptomatology arising from various etiologies; also psychotic patients generally appear not to develop tolerance or supersensitivity to neuroleptics alone.

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In recent years, alterations in receptor sensitivity, especially DA receptor supersensitivity, have been frequently studied in animals and, to an increasing extent, in man. The possible role of DA supersensitivity in schizophrenia and its relationship to previous evidence for DA involvement are selectively reviewed in order to clarify this concept in man and, more specifically, schizophrenia. One hypothesis is that acute schizophrenia is a specific state of illness, viz., psychotic disorganization, associated with an altered physiologic state, viz., DA receptor supersensitivity.

Receptor sensitivity refers to variable receptor response in relation to availability of its neurotransmitter. In those systems studied, in the relative absence of the neurotransmitter, the receptor may become supersensitive, leading to an increased response to a given neurotransmitter stimulus; conversely, when the neurotransmitter is in relative excess, receptor sensitivity may be diminished, with a possible decreased response to a given neurotransmitter stimulus (Meltzer and Stahl 1976). However, recent behavioral evidence indicates receptor supersensitivity may sometimes arise following chronic agonist stimulation (Klawans and Margolin 1975; Post 1978), although the mechanism by which this occurs is not clear. Possibly a large single dose of a drug may lead to a decreased number of receptor sites, whereas a moderate chronic dose may lead to an increased number of receptor sites to accommodate the ongoing pharmacological stimulus. It should be noted, though, that a recent study (Howlett and Nahorski 1979) found an apparently opposite effect following d-amphetamine in rats; after the large acute dose, a significant increase in binding sites did occur, but there was a significant fall in affinity for the labeled ligand. Obviously, there are many difficulties in using behavior as a variable to indicate the dynamics of receptor binding sites. In addition, studies that do not take into consideration the pharmacokinetics of the drug involved, the time course, method, and dose level of administration, the anatomical tracts under study, the adaptability of receptor sites, and the phase of the disorder (e.g., schizophrenia in humans) may be more confusing than clarifying.

This review will begin with the basic laboratory work upon which the concept of DA receptor supersensitivity is based, followed by neuroanatomical considerations, before addressing itself to its application to schizophrenia and clinical studies to be followed by considerations of etiology and future research.

Methods of Induction and Techniques of Ascertainment

If a peripheral nervous system receptor site is deprived of its transmitter, it acquires supersensitivity (a shift to the left of the dose-response curve) to that substance. For example, when the nerve innervating a muscle is cut, receptor supersensitivity ensues, and similarly, after neuronal degeneration, muscle shows greater response to applied transmitter (Thesleff 1960; Trendelenburg 1966). Receptor supersensitivity also occurs in the central nervous system (CNS). Some studies suggest that decreased DA availability at the postsynaptic neuron will lead to increased sensitivity to DA agonists. Evidence that alteration of DA activity by surgical or pharmacologic means can result in "denervation" supersensitivity and that chronic stimulation of DA receptors can lead to "innervation" supersensitivity to subsequent administration of DA agonists is reviewed.

Ungerstedt (1971) demonstrated in rats that if unilateral neostriatal DA pathways are destroyed by injection of 6-hydroxydopamine (6-OHDA) into cell bodies of the substantia nigra, DA receptors still present in the denervated neostriatum show supersensitivity to certain postsynaptic DA agonists (e.g., apomorphine) administered systemically, resulting in contralateral rotational behavior. This behavior, confirmed by others (Von Voigtländer and Moore 1973; Nahorski 1975; Thornburg and Moore 1975; Ungerstedt et al. 1975; Pycock and Marsden 1977), is thought to show an ipsilateral stimulation of supersensitive DA receptors due to degeneration of the afferent nigro-neostriatal pathway.

Motor supersensitivity to DA receptor stimulants is apparent after withdrawal of drugs that reduce DA synaptic activity. Chronic treatment with α-methyl-p-tyrosine (AMPT), a catecholamine synthesis inhibitor, increases behavioral response to direct DA agonists (Tarsy and Baldessarini 1974). Cessation of chronic treatment with reserpine, a catecholamine storage depletor, also leads to behavioral supersensitivity (Tarsy and Baldessarini 1974; Friedman et al. 1975; Ungerstedt et al. 1975). Rats, mice, or guinea pigs treated with the neuroleptic drugs chlorpromazine (Tarsy and
behavior (Klawans and Margolin 1975) and pimozide (Moore and Thornburg 1975) show an enhanced response to the motor stimulant effects of apomorphine. 

Supersensitivity may also follow chronic dopaminergic stimulation, or “innervation” supersensitivity. There is increasing evidence that amphetamine, cocaine, and, perhaps, bromocriptine (a direct DA agonist) may produce supersensitivity to subsequent challenge (Post 1978). After chronic amphetamine treatment, guinea pigs demonstrate an increased sensitivity to both amphetamine- and apomorphine-induced stereotyped behavior (Klawans and Margolin 1975). Hicks et al. (1977) have demonstrated behavioral supersensitivity to apomorphine and methylphenidate after interruption of chronic treatment with bromocriptine or bromocriptine plus levodopa. Flemenbaum (1977) has reported long lasting agonist-induced behavioral supersensitivity in rats following treatment with d- or l-amphetamine or cocaine on alternating days and in increasing doses. Other experimental evidence, as supported by increased number of DA binding sites, adenylate cyclase studies, electrophysiologic measures, neuroendocrine response, and cerebrospinal fluid (CSF) metabolites, is reviewed below.

Studies of Dopamine Receptor Binding Enhancement. Burt, Creese, and Snyder (1977) and Creese, Burt, and Snyder (1977) correlated behavioral supersensitivity following either chronic neuroleptic treatment or 6-OHDA lesions with increased number of DA binding sites; others (Muller and Seeman 1978; Pert et al. 1978) have also correlated behavioral supersensitivity following chronic administration of haloperidol, fluphenazine, and reserpine with increased number of DA binding sites.

Adenylate Cyclase Studies. One action of DA is to increase the synthesis of adenosine cyclic 3', 5'-monophosphate (c-AMP) by stimulation of a specific DA-sensitiv


DA-sensitive adenylate cyclase in cell-free preparations of caudate nuclei not only provided an in vitro model to study the DA receptor but also raised the possibility that postsynaptic DA receptors could regulate the enzyme (Kebabian, Petzold, and Greengard 1972), thus suggesting a mechanism for the response to DA (Kebabian and Greengard 1971). More detailed characterization of the DA receptor associated with the striatal enzyme followed (Kebabian 1978). Mishra et al. (1974) and Satoh et al. (1976) have demonstrated enhancement of DA-stimulated adenylate cyclase in rat caudate following 6-OHDA lesions in substantia nigra; Friedhoff, Bonnet, and Rosengarten (1977) found that rats treated chronically with DA receptor blockers had increased striatal adenylate cyclase and increased 3H-DA binding. Fredholm (1977) demonstrated decreased phosphodiesterase, an enzyme upon which the catabolism of c-AMP is dependent, in rat striatum following chronic haloperidol and suggested that supersensitivity may be due to a decreased degradation rather than an increased formation of c-AMP.

Attempts by Krueger et al. (1976) and Von Voigtländer, Boukma, and Johnson (1973) to relate AMPT- and 6-OHDA-induced supersensitivity to increases in DA-sensitive adenylate cyclase have been unsuccessful; stimulation of c-AMP occurred, but no change in DA-sensitive adenylate cyclase was observed. Rotrosen, Friedman, and Gershon (1975) and Von Voigtlander, Losey, and Triezenberg (1975) failed to observe any changes in striatal adenylate cyclase after administration of several neuroleptics. Quik and Iversen (1978) observed a decrease in c-AMP (despite the presence of a phosphodiesterase inhibitor), but no change in DA-sensitive adenylate cyclase after chronic bromocriptine.

Some of the above apparent inconsistencies and complexities may be clarified by more recent data (Kebabian 1978; Kebabian and Calne 1979). Not all DA receptors are similar to those linked to adenylate cyclase; therefore, in some tissues, a DA-stimulated accumulation of c-AMP would probably not be due to the same mechanisms that are presumably operant in relationship to DA receptors that are linked to adenylate cyclase. DA receptors have been identified at five sites within the nigrostriatal axis. Three are not associated with adenylate cyclase (classified as D-2 DA receptors); two are linked to adenylate cyclase (classified as D-1 DA receptors). In the striatum, (1) presynaptic receptors that control tyrosine hydroxylase are not linked to adenylate cyclase; (2) postsynaptic receptors, which respond to ergot agonists in vitro also are not linked to adenylate cyclase; but (3) postsynaptic receptors are linked to...
adenylate cyclase. In the substantia nigra, (4) presynaptic receptors are linked to adenylate cyclase; but (5) autoreceptors (on the DA nigrostriatal neurons) are not linked to adenylate cyclase.

**Electrophysiologic Studies.** Neuronal sensitivity has been investigated by studying the change in neuronal firing following microiontophoretically applied DA. When the caudate nucleus is DA depleted by intraventricular 6-OHDA, DA itself can further decrease neuronal firing induced by excitant amino acids *in vivo* (Siggins, Hoffer, and Ungerstedt 1974). Similarly, repeated administration of haloperidol enhanced the effect of DA receptor agonists applied directly to single caudate neurons (Yarbrough 1975; Skirboll and Bunney 1978). DA-containing cells in the substantia nigra, following haloperidol (Gallager, Pert, and Bunney 1978) or fluphenazine (Nowycky and Roth 1977), are similarly affected; thus presynaptic receptors may become supersensitive as well. In a recent review of the effects of acute and chronic haloperidol treatment on nigral DA cell activity, Bunney and Grace (1978) suggested that chronic haloperidol increases DA cell activity to the point that they may go into tonic depolarization block; they further suggested that depolarization inactivation from decreased neurotransmitter release, and thus decreased availability at postsynaptic receptors, could be a mechanism for inducing postsynaptic supersensitivity. Acute haloperidol treatment appeared to activate DA cells that are normally inactive and accelerated the firing rate of DA neurons. Klawans and Margolin (1975) demonstrated that chronic amphetamine potentiates apomorphine-induced stereotyped behavior. Groves and Rebec (1977) demonstrated decreased neuronal activity in the striatum and reticular formation from apomorphine following chronic amphetamine pretreatment.

**Studies of Neuroendocrine Response.** Cheung and Weiner (1976) demonstrated supersensitivity to apomorphine of anterior pituitary DA receptors, which inhibit prolactin (PRL) secretion following destruction of medial basal hypothalamus in ovariectomized rats. Increased plasma PRL following medial basal hypothalamic lesions is consistent with previous observations by Arimura, Dunn, and Schally (1972). Following haloperidol treatment on nigral DA cell activity, Bunney and Grace (1978) suggested that chronic haloperidol increases DA cell activity to the point that they may go into tonic depolarization block; they further suggested that depolarization inactivation from decreased neurotransmitter release, and thus decreased availability at postsynaptic receptors, could be a mechanism for inducing postsynaptic supersensitivity. Acute haloperidol treatment appeared to activate DA cells that are normally inactive and accelerated the firing rate of DA neurons. Klawans and Margolin (1975) demonstrated that chronic haloperidol increases DA cell activity to the point that they may go into tonic depolarization block; they further suggested that depolarization inactivation from decreased neurotransmitter release, and thus decreased availability at postsynaptic receptors, could be a mechanism for inducing postsynaptic supersensitivity. Acute haloperidol treatment appeared to activate DA cells that are normally inactive and accelerated the firing rate of DA neurons. Klawans and Margolin (1975) demonstrated that chronic amphetamine potentiates apomorphine-induced stereotyped behavior. Groves and Rebec (1977) demonstrated decreased neuronal activity in the striatum and reticular formation from apomorphine following chronic amphetamine pretreatment.

**Studies of CSF Metabolites.** Studies of acute and long-term effects of neuroleptics have been reviewed (Meltzer and Stahl 1976; Post et al. 1980); no animal studies showing behavioral supersensitivity and describing CSF DA metabolites were noted.

**Existence of Several Dopamine Tracts and Functional Receptor Differences**

DA is localized in discrete pathways that are still being identified and characterized. Evidence exists from histofluorescent and biochemical studies for six distinct DA tracts (Ungerstedt 1974; Lindvall and Bjorklund 1974). The functional anatomy of these tracts and their possible relationship to schizophrenia is reviewed elsewhere (Meltzer and Stahl 1976).

In the nigrostriatal DA tract, studies above have described behavioral supersensitivity to DA agonists following lesions or chronic neuroleptics. Supersensitivity has been correlated with an increased number of DA binding sites. Trabucchi et al. (1976) demonstrated supersensitivity by measuring DA- and LSD-stimulated c-AMP formation in rat retina, both after light deprivation and reserpine-induced depletion of DA.

Cheung and Weiner (1976), above, have demonstrated supersensitivity in the tuberoinfundibular DA tract. Receptors mediating hypothermia may be located in the incertohypothalamic DA tract. Reid (1975) investigated the effects of DA agonists on the colonic temperature in rats at different ambient temperatures. Following DA depletion by intracisternal 6-OHDA and intraperitoneal desmethylimipramine, the intensity and duration of hypothermia were enhanced by administration of piribedil (a direct DA agonist). Kelly and Iversen (1976) demonstrated that selective 6-OHDA destruction of mesolimbic DA-containing terminals in rats led to enhanced apomorphine-induced locomotor activity. Following chronic haloperidol or clozapine, apomorphine was effective in retarding the AMPT-induced depletion of DA in both the striatum and the olfactory tubercle (Gianutsos and Moore 1977). Whether there is a common innervation of both the limbic and cortical area is unknown; the cells of origin appear relatively homogenous as regards drug response (Bunney and Aghajanian 1978). Hokfelt et al. (1974) described innervation to gyrus cinguli, entorhinal cortex, hippocampus, claustrum, amygdaloid cortex, basal layers of dorsal...
frontal cortex, and prepyriform cortex. Studies of supersensitivity in these specific tracts have not been noted.

Friend et al. (1978) suggested that DA receptors respond tract specifically to chronic receptor blockade, i.e., rats pretreated with haloperidol and subsequently withdrawn show decreased \( ^3 \)H-haloperidol binding in the pituitary and increased binding in the striatum. Costentin, Protais, and Schwartz (1975) reported different responses to apomorphine in haloperidol-pretreated mice, i.e., desensitization of DA receptors controlling thermoregulation and supersensitivity in climbing behavior; they were unable to induce supersensitivity of hypothermia and postulated that the receptors mediating hypothermia were, before treatment, already at maximal functional sensitivity, whereas the converse was true of climbing behavior. Perhaps not surprisingly, repeated \( d \)-amphetamine in rats may lead to reverse tolerance (supersensitivity) with regard to motor activity but to tolerance with regard to self-stimulation (Leith and Kuczenski 1979). Kelly, Seviour, and Iversen (1975) studied amphetamine and apomorphine in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Fourteen days after 6-OHDA, low-dose amphetamine failed to induce locomotor responses after nucleus accumbens septi lesions, but did so after caudate lesions. By contrast, the caudate lesions, but not the nucleus accumbens septi lesions, abolished intense stereotyped behavior from high-dose amphetamine. Both groups showed supersensitivity to apomorphine;

the nucleus accumbens septi group showed enhanced locomotor activity, and the caudate group showed enhanced stereotyped behavior. Locomotor activity and stereotypy may be mediated by separate neural systems.

The study of acute and chronic administration of neuroleptics in the rabbit demonstrates that homovanillic acid (HVA) increases in the neostriatum show tolerance (a shift to the right of the dose-response curve) while those in hypothalamic and limbic systems do not (Bowers and Rozitis 1974). Tolerance induction may explain why it is unnecessary to administer anticholinergic drugs to prevent extrapyramidal side effects after a month or so of antipsychotic drug treatment in some neuroleptic-treated psychotics. That HVA in CSF is largely derived from the nigrostriatal system (Sourkes 1973) may relate to the observation that CSF HVA increases in acute neuroleptic treatment, but may be attenuated after chronic treatment (Sedvall et al. 1974; Gerlach, Thorsen, and Fog 1975; Post and Goodwin 1975; van Praag 1977). In a more recent report (Post et al. 1980) of acute pimozide treatment in manics, however, no consistent effect on CSF HVA was noted.

If antipsychotic medication had its effect in the mesolimbic (Snyder et al. 1974; Bunney and Aghajanian 1975a) and mesocortical DA systems, one might expect the clinical observation that tolerance to the antipsychotic effects of neuroleptics rarely occurs. Julou, Scatton, and Glowinski (1976), in rats, have reported differences in acute and chronic response to neuroleptics in different DA tracts. After acute administration, DA synthesis was more in the striatum than in the meso-limbic-mesocortical systems; after chronic administration, however, the converse was true. Scatton (1977) suggests that with repeated neuroleptic administration in rats, tolerance to the increases in DA turnover occurs in the striatum, nucleus accumbens, olfactory tubercle, and frontal cortex; the threshold dose appears to be lower and tolerance develops earlier in the striatum, however, than in the limbic regions and frontal cortex; thus, there may be differential rates of tolerance development in different systems. No tolerance was observed in the retinal system after treatment with neuroleptics, even in high doses (Scatton, Dedek, and Korf 1977); the tuberoinfundibular DA system appears to respond similarly (Fuxe et al. 1976). Since DA control of PRL secretion is thought to be located in the arcuate nucleus of the hypothalamus, lack of receptor change in this system may explain why PRL levels remain high after chronic neuroleptic treatment (Kolakowska et al. 1975; Wilson et al. 1975).

Evidence For and Against Receptor Supersensitivity in Acute Schizophrenia

Acute schizophrenic symptomatology may be associated with DA receptor supersensitivity (Klawans and Margolin 1975; Segal and Janowsky 1978). Actively ill and partially remitted schizophrenics have shown immediate, dramatic intensification of psychotic symptoms after single dose i.v. methylphenidate (.5 mg/kg); but normal volunteers, personality disorders, alcoholics, neurotics, depressives,
and remitted schizophrenics have not shown activation of psychotic symptoms (Janowsky et al. 1973a, 1973b). Janowsky and Davis (1976) and van Kammen et al. (1977) found that low-dose d- and l-amphetamine enhanced psychotic symptoms in some schizophrenics. Connell (1958) noted no development of paranoid symptomatology at doses less than 50 mg amphetamine, although “true” schizophrenics showed an increase in hallucinatory behavior at doses of amphetamine as low as 20 mg. Johnson and Milner (1966) also reported exacerbation of schizophrenic symptomatology following low-dose amphetamine; West (1974) reported the precipitation of psychosis in chronic schizophrenics following chronic low-dose amphetamine use for weight control. In a double-blind, placebo-controlled study, Brambilla et al. (1979) administered the DA agonist L-dopa (2 g + 200 mg carbidopa for 30 days) or apomorphine (1 mg for 15 days) to six male chronic schizophrenics who were not actively ill at the time of study; neither treatment induced worsening of preexisting symptoms or development of hallucinations or delusions. These results could be related to differences in the receptor state in acute versus nonacute phases of the schizophrenic process. In any case, as with some of the animal studies, it would appear that dose level and length of treatment can also be critical variables.

If active psychotics already have supersensitive DA receptors, then the effect of a DA agonist could be sufficient to exacerbate existing psychotic symptoms. Bunney et al. (1979) have recently reviewed the evidence that seven compounds which increase functional DA (amphetamine, methylphenidate, large doses of levodopa, piribedil, lergotrile, disulfiram, and phencyclidine) intensify psychotic symptoms in schizophrenics; however, two drugs (bromocriptine and CF 25-397) were not found to intensify psychotic symptoms in this review. In contrast to low doses, high doses of amphetamine-like drugs (i.e., methylphenidate, amphetamine derivatives, and cocaine) induce psychotic symptoms in presumably nonpsychotic individuals (Segal and Janowsky 1978). Commonly, a paranoid psychosis closely resembling paranoid schizophrenia is produced; Snyder (1973) and others (Connell 1958; Bell 1965) have suggested amphetamine psychosis as a model for paranoid schizophrenia.

Drugs that alleviate schizophrenic symptoms have been shown to bind to the DA receptor (Creese, Burt, and Snyder 1975; Snyder 1976). Creese, Burt, and Snyder (1976) and Seeman et al. (1976) have shown that DA receptor binding correlates with clinical and pharmacological potencies of antipsychotic drugs. Neuroendocrine stimulation techniques may provide a noninvasive method for in vivo assessment of DA function in schizophrenia (Sachar 1975), i.e., stimulation of hypothalamic DA systems releases pituitary growth hormone (GH) into the peripheral circulation (Lai et al. 1975). Pandey et al. (1977a, 1977b) examined postsynaptic DA receptor sensitivity in schizophrenics by using apomorphine-induced GH release; activity of platelet adenylate cyclase was also studied following stimulation by prostaglandin E1; acute schizophrenics had significantly higher GH responses and adenylate cyclase activity than normal controls and chronic schizophrenics.

CSF studies have been inconsistent (Gruen 1978) and may reflect only nigrostriatal DA activity (Sourkes 1973). Bowers (1973, 1974) reported decreased probencid-induced HVA in “poor prognosis” schizophrenics. An inverse relationship between schizophrenic psychopathology and central DA turnover measured by CSF HVA (Bowers 1974; Post et al. 1975) is consistent with DA postsynaptic supersensitivity with compensatory presynaptic inhibition.

Recent literature reviews stress the importance of mesolimbic and mesocortical DA systems in schizophrenia (Torrey and Peterson 1974; Meltzer and Stahl 1976). Schizophrenia-like symptoms occur in temporal lobe epilepsy and in brain tumors affecting the limbic system and/or the cingulate gyrus (Malamud 1967); similarly, “injury” of mesocortical structures may lead to schizophrenia-like symptoms. Whether such disorders support DA receptor supersensitivity in schizophrenia is not clear.

DA receptor binding in autopsied brains of schizophrenics and controls has been measured. Lee et al. (1978) and Owen et al. (1978) reported increased H-spiroperidol binding in the nucleus accumbens, putamen, and caudate of schizophrenics vs. controls. H-spiroperone, which reflects both DA and serotonin (5HT) receptor binding, was unchanged in the nucleus accumbens in schizophrenics vs. controls (MacKay et al. 1978). Increased H-haloperidol binding has also been reported in
these same brain areas; $^3$H-apomorphine binding was not significantly different in schizophrenic patients vs. controls (Lee et al. 1978). Why $^3$H-haloperidol binding does not change and $^3$H-apomorphine does may be explained by evidence that $^3$H-apomorphine has a predilection for presynaptic DA receptors (Nagy et al. 1978). Low doses of apomorphine do not exacerbate but may actually alleviate some psychotic symptoms (Angrist et al. 1975; Tamminga, Schaffer, and Smith 1978). Any interpretation of the apparently increased number of receptors in the schizophrenic brains would have to take into consideration drug history: most patients in these studies had recently received neuroleptics, although binding was also elevated in one who was reported to have been drug-free 5 years, and in another who apparently had never received neuroleptics. The above studies suggest that DA receptor binding in schizophrenic patients may differ from that in normal human brains, but it is not yet known whether the increase in DA receptor binding is related to state or trait (not that these two conditions within themselves would necessarily remain constant throughout a lifetime of fluctuations and change in the disorder itself).

While the studies cited above documented that amphetamine or methylphenidate can exacerbate psychotic symptomatology in acute schizophrenics, Van Kammen et al. (1977), in a double-blind, placebo-controlled study, reported temporary improvement in some acutely psychotic schizophrenics following i.v. infusion of 20 mg of d-amphetamine. The authors hypothesize that there may be a differential effect on presynaptic versus postsynaptic receptors, that amphetamine may have been stimulating inhibitory DA receptors, or that amphetamine is temporarily affecting a feedback regulatory process.

Tuberoinfundibular DA neurons exert a tonic inhibitory effect on PRL secretion (Fuxe and Hokfelt 1969; Hokfelt and Fuxe 1972). If plasma PRL reflects brain DA activity, then PRL should be low in schizophrenics. Meltzer, Sachar, and Frantz (1974) reported that baseline PRL values were not different between newly admitted schizophrenics and controls; they then showed that day of admission plasma PRL in schizophrenics was significantly higher than subsequent determinations. Gruen (1978) suggests that there is an initial acclimatization response and then a return to baseline PRL levels; he concludes that both baseline PRL and responses to DA antagonists and agonists fail to show any differences between schizophrenics and normals. Tamminga et al. (1977) and Ettigi et al. (1976) studied PRL and GH response to apomorphine and levodopa in chronic schizophrenics with tardive dyskinesia and demonstrated no evidence of supersensitivity. While the lack of change in PRL in acutely psychotic schizophrenics is evidence against the occurrence of DA receptor supersensitivity in the tuberoinfundibular system, one cannot necessarily rule out supersensitivity in the mesolimbic and mesocortical systems; likewise, nigrostriatal DA receptor supersensitivity cannot be ruled out in tardive dyskinesia because of normal PRL and GH response.

Clinical and Physiological Considerations

The DA receptor, in the course of time, can show altered receptor sensitivity to drugs that affect DA metabolism. DA receptor supersensitivity may offer generative clues to the pathogenesis of certain psychiatric and neurologic illnesses such as schizophrenia. Although psychiatry has often focused on schizophrenia as a static and relatively independent structure, clinical observation evinces that major psychiatric disorders are dynamic and may overlap. Often there seems to be a prodromal history—a period of progressive psychological and biological dysfunction. A study of the stages of onset of schizophrenic psychosis (Docherty et al. 1978) indicates that the psychosis is but one stage in a process of psychological breakdown which has a specific structure and characteristic unfolding. This structure appears to consist of the sequential appearance of hierarchically ordered, distinguishable psychologic states. Speculations may be made related to the processes which might underlie this progressive sequence; DA receptor supersensitivity may provide a useful perspective.

Post and Kopanda (1976) have reviewed evidence that repetitive but intermittent administration of stimulant drugs is associated with increasing pathological behavior, not tolerance; this progression may be related to kindling, a phenomenon in which repetitive but intermittent subthreshold stimulation of the limbic system comes to be associated with major motor seizures. Induction of DA receptor supersensitivity by physiological, or possibly psychological, means
would not be incompatible with a kindling-like mechanism.

Although high doses of i.v. amphetamine lead to rapid onset of psychosis, Bell (1973), Griffith et al. (1972), and Angrist and Gershon (1970) report that moderate doses over several days lead to a progressive, rather than sudden, onset of psychosis. According to Charles-Nicholas (1976), 30 percent of i.v. amphetamine users who suffer acute toxic psychoses go on to develop chronic psychotic states (without prior history of psychosis). Psychotic symptoms may be progressively enhanced by a DA agonist, though tolerance develops to the euphoriant action (Angrist and Gershon 1970; Griffith et al. 1972); this report is not inconsistent with those animal studies in which both reverse tolerance and tolerance for different behaviors develop from the same regimen of d-amphetamine (Leith and Kuczenski 1979). Amphetamine users do not usually develop paranoid psychosis until the third or fourth day of use (Kramer, Fischman, and Littlefield 1967), but amphetamine users who have experienced drug-induced psychosis in the past may experience almost immediate recurrence of paranoid psychosis, despite prolonged abstinence (Angrist and Gershon 1970; Kramer 1972; Bell 1973). Drug abusers take amphetamines and/or cocaine cyclically in an "on and off" pattern, with a tendency to increased dosages followed by periods of no drug intake (Flemenbaum 1977); is such a method of administration a self-induced kindling?

Moskovitz, Moses, and Klawans (1978) evaluated randomly selected patients with idiopathic Parkinson's disease, but without a history of psychotic symptomatology, for the occurrence of psychotic symptoms as side effects of chronic levodopa therapy. A progression of medication-induced mental symptomatology was observed, from striking dreams to hallucinatory experiences, to a pure paranoid delusional system, all with a clear sensorium, and finally to a confusional toxic paranoid psychosis. The major underlying factor in most cases appeared to be duration of levodopa therapy.

Sweet et al. (1972) provide further evidence that repetitive stimulation with DA agonists may lead to the development of DA receptor supersensitivity, viz., an enhanced response to low doses of levodopa after withdrawal from chronic treatment, and Lin and Ziegler (1976) describe the initial onset of psychotic symptoms in two patients in whom chronic levodopa treatment was temporarily discontinued, following which a combination of levodopa-carbidopa was initiated. Lipper (1976) described a Parkinsonian patient treated chronically with bromocriptine and levodopa-carbidopa; one week after bromocriptine was discontinued and the dose of levodopa-carbidopa increased, the patient became psychotic. Psychotic symptoms were still present after 1 year despite a decrease in levodopa-carbidopa. Had chronic treatment induced DA receptor supersensitivity, the manifestations of which were controlled when both the direct and the indirect DA agonists were being given? The studies cited above suggest a persistent structural change at the DA receptor following agonist stimulation. Altered sensitivity of specific DA receptors (Stevens 1972; Hokfelt et al. 1974; Stevens, Wilson, and Foote 1974) is a possibility for schizophrenia as well as tardive dyskinesia (Klawans and Rubovits 1972).

Etiological Considerations

The existence of both genetic and environmental factors in the etiology of schizophrenia is highly probable (Rosenthal and Kety 1968, Gottesman and Shields 1972, 1976, Matthysse and Kidd 1976). Therefore, a hypothesis of onset of the acute psychotic episode in schizophrenia might need to take into account biological—genetic and acquired—psychological, and environmental factors. Segal, Geyer, and Weiner (1975) reported strain differences in rat catecholamine postsynaptic receptor sensitivity. Genetic differences in DA receptor sensitivity may alter the likelihood of developing schizophrenia, as well as pharmacological response to agents that alter DA metabolism. A number of basal ganglia disorders including torsion dystonia (Eldridge 1970), Gilles de la Tourette's syndrome (Pollack, Cohen, and Friedhoff 1977), and Huntington's disease (Klawans, Paulson, and Barbeau 1970; Klawans 1973; Klawans and Weiner 1974) may be related to a genetically determined alteration in central DA activity.

Pollack, Cohen, and Friedhoff (1977) and Nee et al. (1980) have reported within-family studies of Gilles de la Tourette's syndrome, both of which suggest a familial component. Golden (1974) and Denckla, Bemporad, and MacKay (1976) have described children in whom Gilles de la Tourette's syndrome developed following the treatment of hyperactivity with
methylphenidate. Huntington’s disease is an autosomal dominant-inherited disorder, with onset generally after the age of 30, whose pathophysiology is thought to involve an increased response of striatal neurons to DA (Klawans 1973). Klawans, Paulson, and Barbeau (1970) have reported that levodopa stimulation of these presumably supersensitive DA receptors in asymptomatic patients can bring out previously undetected chorea and is predictive of the eventual appearance of the illness. Klawans and Weiner (1974) have recently reported that a single i.v. dose of 10 mg/kg amphetamine is sufficient to exacerbate or uncover chorea in patients with Huntington’s disease, Sydenham’s chorea, or chorea associated with systemic lupus erythematosus, but not in normal controls. Other studies (Caraceni et al. 1977; Hayden et al. 1977; Caine et al. 1978) point also to disordered neurotransmitter and/or receptor function in the hypothalamic-pituitary axis of patients with Huntington’s disease. Exogenous influences on DA receptor sensitivity may also precipitate schizophrenic symptoms in those individuals who may be genetically predisposed.

Acute schizophrenia has been associated with an increased number of recent life events and crises (Brown and Birley 1968; Steinberg and Durell 1968; Birley and Brown 1970; Jacobs and Myers 1976). The variations in number, severity, and pattern of recent life events in schizophrenics suggest a precipitant role for the disorder rather than a causative one (Jacobs and Myers 1976). Receptor sensitivity in the mesolimbic and mesocortical DA systems might be progressively altered by repetitive stressful episodes—akin to DA agonist repetitive stimulation, possibly in the manner from which kindling results. This concept is supported by studies which demonstrate that effects of experimental stress on biogenic amines in animals and man can be similar to those produced by psychomotor stimulants (Weil-Malherbe and Szara 1971).

To assess the role of maternal stress during pregnancy on the offspring’s risk for psychiatric disorders, Huttunen and Niskanen (1978) conducted a retrospective study of persons whose fathers had died (viewed as a maternal stress) during the child’s gestation; the control group comprised persons whose fathers had died during the first year of their lives. The number of hospitalized and diagnosed schizophrenics was significantly higher in the index versus the control group; these results may suggest that maternal stress during pregnancy is associated with risk for schizophrenia. Other human studies indicate that pregnancy and birth complications may have an important etiological role in schizophrenia (Pollin and Stabenau 1968; Mednick 1970; Handford 1975). Animal research has also demonstrated that prenatal events can profoundly affect neuronal function and behavior of offspring (Joffe 1969; Huttunen 1971; Dorner 1974). Handford (1975) has reviewed a possible relationship between brain hypoxia, minimal brain dysfunction, and schizophrenia. Prenatal, perinatal, or immediately postnatal hypoxic damage to the dopaminergic pathways could result in altered receptor sensitivity (supersensitivity?) to locally released DA.

Matthysse and Matthysse (1978) have recently reviewed the evidence that immunologic and virus-induced events may be contributory factors in schizophrenia. Studies of patients with myasthenia gravis have demonstrated that autoimmune processes can specifically affect neurotransmitter receptors (Fambrough, Drachman, and Satyamurti 1973); viruses that affect specific cell types presumably attach to a distinctive receptor on the surface of the target cell (Matthysse and Matthysse 1978).

**Future Research**

Considerable evidence could indicate that an acute psychotic episode in schizophrenia is associated with tract and/or systems-specific DA receptor supersensitivity. The DA hypothesis of schizophrenia has had considerable heuristic value; indeed, this hypothesis has stimulated a number of basic and clinical scientists to investigate the anatomy, biochemistry, and physiological function of DA as it might relate to behavior, particularly schizophrenia. However, the DA hypothesis in its simplest form, while assuming functional changes in the availability of DA to the receptor, probably also tacitly assumes a receptor that is static rather than dynamic.

Recent research encourages the reassessment of this hypothesis with a focus on the physiological state of the DA receptor during various behavioral states of the schizophrenic process. Characterization of DA receptors has been possible only relatively recently (Creese and Snyder 1978). Further exploration of DA receptor binding and receptor-adenylate cyclase in-
teractions (Creese et al. 1977; Kebabian 1978) may provide information that could tentatively be linked to behavior (Fambrough, Drachman, and Satyamurti 1973) and its pharmacological alteration (Kebabian 1978; Kebabian and Calne 1979). More specific research is necessary to explain the variations observed in the pharmacological induction of DA receptor sensitivity. Highly controlled pharmacokinetic studies with variations in dose, treatment interval, and method of administration might clarify some of the current apparent inconsistencies; these should include repetitive, blind, crossover studies in which subjects are used as their controls, as well as more rigorous studies with distinct experimental and control groups. Recent data (Kehr et al. 1972; Bunney and Aghajanian 1975b; Strömbo 1976) suggest that there are at least two general sets of DA receptors: receptors located on dendrites, cell bodies, and presynaptic terminals (sometimes referred to as autoreceptors), and a second set innervated by the DA system (often referred to as postsynaptic receptors). Evidence that low doses of agonists may activate presynaptic mechanisms, leading to inhibitory effects of DA transmissions (Roth, Walters, and Mogenroth 1974; Carlsson 1975; and Strömbom 1976), and the concept of dendritic release (Bjorklund and Lindvall 1975; Groves et al. 1975) require further study. Interactions between DA systems themselves, as well as between DA systems and other neurotransmitter and neuropeptide systems, also will need to be better understood.

From a therapeutic perspective, Friedhoff and Alpert (1978) have recently been interested in receptor sensitivity modification as a potential treatment. Rats treated chronically with neuroleptics were found to have an increase in striatal \(^3\)H-DA binding and adenylate cyclase activity—presumed manifestations of DA receptor supersensitivity; both findings were reversed by chronic levodopa treatment, possibly due to increasing the supply of DA (Friedhoff, Bonnet, and Rosengarten 1977). Friedhoff and Alpert (1978) have recently reported reversal of oral dyskinesia in one patient and of tardive dyskinesia in another, as well as improvement of motor tics in a patient with Gilles de la Tourette syndrome after levodopa treatment and subsequent withdrawal. Whether such presumed supersensitivity, if it indeed occurs in some phases of schizophrenia, could be "desensitized" is an unresolved question.

It is hoped that the ever-increasing and more specific understanding of CNS DA function, despite some of the inconsistencies from research to date, will further stimulate an understanding of the biological contributions to schizophrenia. Angrist, B.; Thompson, H.; Shopsin, B.; and Gershon, S. Clinical studies with dopamine-receptor stimulants. Psychopharmacologia, 44:273-280, 1975.


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