Variability and the Dopamine Hypothesis of Schizophrenia

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Abstract

The dopamine hypothesis of schizophrenia is usually presented in a static, rather than dynamic fashion. We propose that increased dopaminergic activity may represent a stage of a dynamic schizophrenic process rather than its cause. Dopamine, as well as other neurotransmitters, responds in an adaptive fashion to stimuli that perturb the homeostasis of the brain. One such stimulus could be an epileptic focus in the temporal lobe. Other such stimuli undoubtedly also exist.

The clinical course of schizophrenia is highly variable. The onset of symptoms may be sudden, or slow and insidious. Spontaneous partial and temporary remissions are common, and in some cases complete and permanent remissions can occur (Ciompò 1980). Biological parameters such as body weight, response to neuroleptic medication, and hormonal activity can also vary spontaneously in the course of the disease (van der Velde 1976). Despite evidence of clinical and biological variability, some hypotheses concerning the neurochemical etiology of schizophrenia, such as the dopamine hypothesis, have proposed a single persistent abnormality.

The dopamine hypothesis of schizophrenia postulates an overactivity of dopamine in the mesolimbic system of the brain. Support for this hypothesis has been proposed by demonstration of increased $^3$H-spiroperidol binding, presumably reflecting dopamine receptors, in the nucleus accumbens, the caudate nucleus, and the putamen of post-mortem schizophrenic brains (Lee et al. 1978; Owen et al. 1978). The interpretation of these reports is confounded, however, by the fact that prior neuroleptic treatment might be the cause of these findings (Mackay et al. 1980, 1982). However, such findings have also been reported in neuroleptic-naive patients (Lee and Seeman 1980) and are said to be associated with a particular subtype ($D_2$) of dopamine receptor (Cross, Crow, and Owen 1981). The presumed increased dopamine receptor binding may not necessarily result in an overactivity of dopaminergic function. Reciprocal changes presynaptically such as decreased dopamine synthesis or release might counterbalance, or perhaps cause, increased postsynaptic receptor binding. Thus, a change in dopamine receptors might be interpreted as a stage in the fluctuation of a disordered dopaminergic system.

Clinical studies suggest variability in dopamine function in schizophrenia. Alpert et al. (1978) reported slight improvement in thought disorder in seven schizophrenics treated with levodopa. Based in part on differences in schizophrenics' responses to levodopa, Alpert and Friedhoff (1980) suggested that there may be diverse disorders of dopamine function in schizophrenia. Angrist, Rotrosen, and Gershon (1980) observed differences in the responses of schizophrenics to amphetamine and neuroleptics. In 14 of 21 schizophrenics, symptom exacerbation occurred after a single dose of amphetamine and was correlated with a favorable neuroleptic response. In the remaining seven patients, no effect or slight improvement was noted. Van Kammen et al. (1982) reported that symptom improvement in response to dextroamphetamine paradoxically predicted a favorable response to...
neuroleptics. One implication of these studies is that schizophrenia is a heterogeneous disorder. However, it is also possible that neurochemical variability occurs within a single individual with schizophrenia (Van Kammen et al. 1982) and that individual variability in dopamine function over a lifetime results in apparently heterogeneous patient groups. Whatever the nature of such variability in schizophrenia, it is clear that a hypothesis for the etiology of schizophrenia proposing a single, fixed neurochemical lesion is unlikely. The clinical and neurochemical variability discussed above suggests the need for a more dynamic model.

**A Dynamic Biochemical Model of Schizophrenia**

The brain must be viewed as dynamic and interactive, capable of ongoing adaptive change. Luria (1973) proposed a 'working' view of the brain as a collection of functioning systems, each one integrating several brain areas. A dysfunction (e.g., overactivity) in one area of a system might bring about adaptive changes in other areas to reestablish a functioning equilibrium. Adaptive changes needed to maintain a functional equilibrium may also occur within a single synapse. For example, blockade of postsynaptic dopamine receptors by neuroleptic drugs can bring about a postsynaptic receptor supersensitivity to overcome the blockade (Friedhoff and Alpert 1978; Muller and Seeman 1978; Klawans, Goetz, and Perlik 1980). Alterations of presynaptic autoreceptors and tyrosine hydroxylase in response to neuroleptic blockade may occur as well (Roth, Salzman, and Nowycky 1978). Considering such plasticity of brain function, the increased postsynaptic dopamine receptor binding that has been reported may represent a needed adaptation. If such were the case, one might expect even further changes in dopaminergic presynaptic function, or possibly changes in other areas or other neurotransmitters. As adaptive neurochemical changes can take days or weeks to develop (Friedhoff and Alpert 1978), such ongoing alterations in synaptic function could cause a slow waxing and waning of schizophrenic symptoms.

If increased dopamine receptor binding is part of an ongoing mechanism of neurochemical adaptation, where does the process originate? Clearly, the answer to this question is complex, as many origins and mechanisms are possible. For example, the nucleus accumbens is one area of the schizophrenic brain where increases in dopamine receptor binding have been observed. However, the nucleus accumbens is part of a large limbic functional system, modulated by the mesolimbic dopaminergic pathway. Other limbic structures such as the amygdala and hippocampus are functionally related to the accumbens. As temporal lobe structures have been proposed as a site for schizophrenic pathology (Stevens 1980), could abnormal functioning of the temporal lobe be the origin of the neurochemical changes in dopamine function seen in the nucleus accumbens?

**Temporal Lobe Epilepsy: A Related Disease?**

Slater, Beard, and Glithero (1963) noted a relationship between temporal lobe epilepsy and a schizophrenia-like psychosis. In their study, the onset of the psychosis, in many cases indistinguishable from schizophrenia, always followed the onset of epilepsy. The psychosis appeared insidiously in patients whose premorbid personalities were unremarkable, who had no family history of psychosis, and whose seizures were decreasing in frequency. Their hypothesis was that in these patients a schizophrenia-like psychosis had evolved as a result of the temporal lobe epilepsy. However, a cause-and-effect relationship between temporal lobe epilepsy and schizophrenic symptoms has been subsequently questioned, and one alternate hypothesis is that these schizophrenic symptoms represent an interictal behavioral syndrome, clinically distinct from schizophrenia or other major functional psychoses (Waxman and Geschwind 1975).

Although the clinical relationship between temporal lobe epilepsy and schizophrenia remains unclear, the proposal by Slater, Beard, and Glithero of a cause-and-effect relationship has generated hypotheses about the pathogenesis of schizophrenia. Trimble (1977) noted the important role of dopamine in both schizophrenia and epilepsy. Stevens (1980) suggested that there may be a link between a temporal lobe epileptic focus, an adaptive blockade to seizure spread, and an increase in dopaminergic function or sensitivity.

To investigate this proposed relationship, we developed a rat model of temporal lobe epilepsy using intra-amygdaloid injections of FeCl₃, in which changes in dopamine function were observed (Csernansky et al. 1983). An asymmetric behavioral dopaminergic supersensitivity was observed several days after the FeCl₃ injection, demonstrated by increases in apomorphine-induced stereotypes and circling toward the side of the focus, as well as continued temporal lobe seizures. We
noted an increase in dopamine receptor (i.e., $^3$H-spiroperidol) binding in the nucleus accumbens ipsilateral to the epileptic focus, and in the amygdala and striatum contralateral to the epileptic focus. The increase in dopamine receptor binding in the accumbens may be related to a blockade of seizure spread, as the function of the ascending mesolimbic dopamine pathway may be to inhibit excitatory output from the amygdala to the nucleus accumbens (Yim and Mogenson 1982). Although we concluded that a temporal lobe epileptic focus could trigger increases in dopamine receptor binding, the experiment was not designed to look further into subsequent ongoing neurochemical adaptations. Such experiments, and experiments to examine spontaneous alterations in dopamine function, are needed.

In summary, we feel that no single neurochemical lesion explains schizophrenia. We propose a dynamic model of schizophrenia, in which waxing and waning symptoms may reflect a series of neurochemical changes within the limbic system. Although dopaminergic overactivity may be an important stage in the evolution of schizophrenia, the origin and eventual outcome of the disease may involve biochemical alterations in other areas of the brain. Changes in related neurotransmitters such as serotonin, acetylcholine, norepinephrine, and the neuropeptides are possible. This dynamic model proposes that intra-individual biochemical variations during the course of illness result in the puzzling biochemical heterogeneity observed in cross-sectional samples of schizophrenic patients.

References


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