

New Models of the Pathophysiology of Schizophrenia: Editors' Introduction

by John G. Csernansky and Anthony A. Grace

Abstract

New models of the pathogenesis of schizophrenia are presented. These models represent hypotheses intended to stimulate discussion and new experimentation. Each of the contributions approach the pathophysiology of schizophrenia from a unique perspective. Yet, all of them emphasize the integration of new advances in basic neuroscience, the functional neuroanatomy of schizophrenia, and information drawn from new biotechnologies, such as neuroimaging and molecular genetics, to provide unique insights into schizophrenia. In each case, the novel hypotheses proposed also illustrate the continuing need for a better understanding of the dynamic interaction between synaptic plasticity and neural circuitry to further our understanding of the human brain in health and disease.

Key words: Dopamine, synaptic plasticity, neural circuitry, neuroimaging.

Schizophrenia Bulletin, 24(2):185–187, 1998.

Before the discovery of antipsychotic drugs, the study of schizophrenia was largely confined to investigations of psychological dynamics or to simple descriptive nosology. While some experts believed that schizophrenia had a biological basis within the brain, there was little evidence to directly support this point of view and to stimulate meaningful research. The discovery of antipsychotic drugs, such as chlorpromazine and haloperidol, in the early 1950s had a tremendous impact on the treatment of schizophrenia. Long-term inpatient stays became increasingly uncommon, and the challenges of treating patients with schizophrenia began moving from the inpatient to the outpatient arena (Csernansky, in press). However, the discovery of antipsychotic drugs also had a major impact on our conceptualization of schizophrenia. For the first time, firm evidence existed that schizophrenia had a physical basis and that physiological modes of intervention

could be employed to treat the disorder (Meltzer and Stahl 1976).

In the 1960s and 1970s, our understanding of the pathophysiology of schizophrenia was generally organized around concepts of neurotransmitter dysfunction with an emphasis on the neurotransmitter dopamine (Moore and Bloom 1978). This focus on a dysfunction in neurotransmission within a single chemical domain was likely influenced by recent success in the etiology and treatment of Parkinson's disease. Unfortunately, initial formulations of the dopamine hypothesis of schizophrenia were overly simplistic, conceiving of schizophrenia's causes as generalized increases in the release of dopamine or to a hypersensitivity of postsynaptic dopamine receptors (Meltzer and Stahl 1976). At that time, relatively little was known about the neuroanatomy of most neurotransmitter systems, and it was generally believed that neurotransmitter dysfunction in schizophrenia occurred within a brain in which normal neuroanatomical structure was preserved. From this era came the popular notion that a "chemical imbalance" was the basis of schizophrenia.

A variety of scientific findings led to more advanced concepts of the pathophysiology of schizophrenia in the 1980s. Basic research brought us new information about chemical neuroanatomy, and an appreciation for the enormous complexity of the brain's neural circuitry emerged (Alexander et al. 1986; Graybiel 1990). In addition, many of the basic elements of synaptic function were elucidated, including rapidly growing lists of neurotransmitter receptor subtypes for many neurotransmitters, including dopamine (Seeman 1980). Of equal importance, post-mortem studies and in vivo neuroimaging studies of the brain began to demonstrate a variety of neuroanatomical abnormalities in patients with schizophrenia (Reynolds 1989). It became clear that simple models of the dysfunc-

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tion or dysregulation of single neurotransmitter systems were inadequate to account for the pathophysiology of schizophrenia (Stevens 1973).

Models of neurochemical imbalance have begun to give way to models of disturbed neural circuitry in our attempts to understand the pathophysiology of schizophrenia (Carlsson 1988; Reynolds 1989; Carlsson and Carlsson 1990; Csernansky et al. 1991; Csernansky, in press). These new models have begun to take into account the interplay among different neurotransmitter systems and the complexity of different modes of neurotransmitter release and receptor responses (Grace 1991). In addition, concepts of neurodevelopment, including the genesis and programmed death of individual neurons throughout the life cycle are now being integrated into these new pathophysiological formulations (Weinberger 1987).

One may reasonably ask why it is necessary to have models or hypotheses of the pathophysiology of schizophrenia. Certainly, it is likely that whatever models we develop today will be supplanted by more advanced ones as our understanding of brain function expands. Our knowledge of brain neurocircuitry and physiology is still grossly incomplete in many areas, and technologies to directly examine brain anatomy and function in living human beings still have many limitations. Thus, one might argue that the field should remain in a fact-finding or exploratory mode and that the acquisition of new knowledge about the brain and schizophrenia is the most efficient way to proceed. However, research is not so much a random process as it is a guided attempt to formulate and test hypotheses; indeed, this is the fundamental basis of the scientific method. Productive research should be hypothesis driven, with the understanding that hypotheses are constructed to be disproven. As each model of pathophysiology gives way to another that can better account for the experimental data, our understanding of the biological basis of schizophrenia and the tools available to treat this disabling disease will improve. Specific pathophysiological models can point the way to brain areas and elements of synaptic mechanisms that need further study, while still providing ample opportunities for general discoveries about the basic mechanisms of brain function.

The pathophysiological models proposed in this issue of the *Schizophrenia Bulletin* have been inspired in various ways. Some were derived from advances in our understanding of basic neuroscience and seek ways to apply this new knowledge to understanding the pathophysiology of schizophrenia. Others represent attempts to organize our current stock of in vivo physiological and clinical findings into a coherent picture of the mechanisms that form the pathological underpinnings of schizophrenia. Still others emphasize the accumulating results of

painstaking postmortem studies of the schizophrenic brain. Finally, other formulations place an emphasis on current opportunities to exploit advances in molecular genetics and neuroimaging in order to bring new perspectives to the problem.

It is hoped that this issue of the *Bulletin* can form a basis for evaluating the current state of our understanding of the pathophysiology of schizophrenia. The sophistication of these pathophysiological models reflects the strengths and weaknesses of current experimental tools and findings. We certainly hope that the availability of new information about the neurobiology of the brain, and new technologies to investigate brain structure and function, will soon reveal the shortcomings of these models and push the field forward. The goal of this issue of the *Bulletin* is to stimulate further discussion and research at both basic and clinical levels, for it is through such research that our ability to diagnose and treat the most disabling of all psychiatric disorders will improve.

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including those that might seem to be radical notions. We welcome all comments.—*The Editors*.

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