ELSEVIER

EDITORIAL

Neuropharmacology in the Next Millennium: Promise for Breakthrough Discoveries

Pharmacology has provided powerful tools to study and characterize neurochemical pathways in the brain, and how these pathways may be involved in the pathophysiology and treatment of psychiatric illness. This work has focused largely on neurotransmitter systems, including the synthesis, release, and metabolism of monoamines and receptor subtypes that control presynaptic release of neurotransmitters and their postsynaptic effects. In addition, pharmacological tools have been useful for developing models of certain neurobiological disorders. However, little progress has been made over the past 40 years in the development of novel therapeutic agents (an exception is the recent finding that a neurokinin-1 receptor antagonist has antidepressant efficacy), and the underlying etiology of psychiatric illnesses has remained largely unknown. This is undoubtedly a result, in part, of the complex nature of disorders of the brain, combined with the fact that most of these disorders are syndromes and are thought to have multiple underlying determinants. Another factor contributing to this problem is that the therapeutic action of most psychotropic agents is dependent on long-term treatment and the consequent molecular and cellular adaptations that occur over time. Thus, future progress in development of novel therapeutic agents and identification of the etiology of psychiatric illnesses will be dependent upon basic and clinical research to characterize the complex neurobiology underlying these disorders.

Complex disorders, such as depression and schizophrenia, involve multiple brain regions and interactions among these regions as well as other areas. This makes it extremely difficult to pinpoint the primary pathophysiological determinants of these disorders. This also poses difficult problems for identifying drug targets and developing efficacious therapeutic agents. On the one hand, the target should be a specific receptor subtype (or subtype of some other signaling protein or enzyme), although most receptors and isozymes are expressed in more than one brain region making this very difficult. This also poses problems for pharmacological studies where drugs are often administered peripherally and have access to the entire brain. On the other hand, the therapeutic efficacy of a drug may be enhanced by its ability to influence multiple receptor or enzyme subtypes. A good example of this is the atypical antipsychotic clozapine, which antagonizes multiple monamine receptor subtypes. This combination of receptor actions is thought to account for the superior efficacy of clozapine, as well as other putative atypical antipsychotics, relative to more selective agents (e.g., selective dopamine D4 receptor antagonists). However, the nonselectivity of clozapine (or olanzapine, for example) most likely also accounts for its side effects, including increased weight gain. Nevertheless, these agents provide an example of how drugs of the future may have a spectrum of neurochemical targets that together result in a greater efficacy and reduced time lag.

The second complication in understanding the action of psychotropic drugs is the requirement for chronic treatment. This has led to the hypothesis that the therapeutic action of these treatments is dependent on adaptations to the acute drug actions (e.g., blockade of monoamine reuptake or metabolism for antidepressants, or antagonism of monoamine receptor subtypes for antipsychotic agents). Identification of the relevant adaptations, which can be thought of as a form of drug-induced neural plasticity, could occur at several cellular levels, including regulation of neurotransmitter receptor coupling and intracellular signaling pathways that control virtually every aspect of neuronal function. The complexity of possible adaptations of these pathways is at least comparable to that of the complex neural circuitry involved in drug action and etiology of psychiatric illnesses. However, this is a very exciting area of research because, like the synaptic plasticity that underlies

NEUROPSYCHOPHARMACOLOGY 1999–VOL. 20, NO. 2

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/99/$–see front matter
PII S0893-133X(98)00105-5

learning and memory, characterization of drug-induced plasticity will provide vital information on how different brain systems adapt to sustained stimulation or inhibition. This information, in turn, will provide novel targets for the development of therapeutic agents. Moreover, this information will be critical for understanding the etiology of complex psychiatric illnesses that are influenced by different environmental factors which could have a major impact on neural adaptive mechanisms. For example, it is likely that adaptive plasticity of a neuronal system is critical to the development of normal responses to environmental inputs, including physical as well as psychosocial challenges. A breakdown in the ability to mount the appropriate adaptive responses could contribute to the etiology of certain disorders. This breakdown could occur for a variety of reasons, including environmental and genetic factors. In either case, further characterization of the mechanisms underlying neural plasticity to drugs, as well as environmental stimuli, will be essential to a better understanding of the molecular and cellular basis of drug action and disease etiology.

Characterization of the neurobiological mechanisms that underlie neural plasticity, as well as the the neural circuitry that conveys this information, is no small task. In addition, identification of the pre- and postsynaptic receptor subtypes and isozymes that acutely control neural plasticity and that may be relevant substrates for the development of therapeutic intervention represents a significant challenge. However, significant technical and conceptual advances have been made at all levels of neurobiology that will enable the success of these goals to be achieved during the next millennium. Advances in molecular gene engineering now make it possible to knock-out and then rescue a gene and to study the cellular and behavioral phenotype of the gene alterations. Moreover, new strategies have been developed for inducible and region specific expression or knock-out of genes. This avoids complications that are encountered in traditional knock-out and transgenic strategies, including the developmental adaptations which occur and the indirect actions that the altered gene may have via its effects on other tissues or brain regions. Neurotropic-viral expression systems have also proven to be extremely useful for inducing localized expression of a gene product. Although these strategies are not routine, they are rapidly spreading and becoming more readily available. For example, it is now possible to order genetically engineered mice from one of several animal vendors that act as clearing houses for research laboratories. Similarly, it is only a matter of time before viral expression systems are available commercially. In combination with the continued development of drugs with different receptor subtype or isozyme profiles, it will be possible to selectively increase or decrease the function of a membrane or cytoplasmic protein and thereby determine its cellular and behavioral actions. The application of these approaches offers tremendous optimism for major breakthrough discoveries in neurobiology. With these advances, in combination with genetic analysis of psychiatric disorders and continued progress in brain imaging, the next millennium will witness a new era of psychiatry as it becomes a fullfledged partner to molecular medicine. This multidisciplinary approach to understanding the neurobiology and pharmacology of psychiatric disorders is also particularly appropriate and well suited for the goals of *Neuropsychopharmacology*.

Ronald S. Duman, Ph.D.
Associate Professor of Psychiatry and Pharmacology
Yale University School of Medicine
New Haven, Connecticut