Emerging Strategies in Neuroprotection

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Foreword by Solomon H. Snyder

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Foreword

SOLOMON H. SNYDER

Receptor Research Reaches Neurology: Relevance to Neurodegenerative Diseases and Stroke

President George Bush has heralded the 1990s as the decade of the brain, based largely on the rapid escalation of advances in the molecular neurosciences and the likelihood that these will bear therapeutic fruit before the turn of the century. There is little doubt that the 1970s and 1980s have witnessed more remarkable advances in the molecular neurosciences than all of the preceding hundred years. Identification of receptor sites for drugs and neurotransmitters along with simple, sensitive, and specific means of monitoring them has made it possible to elucidate the mechanism of action for many known drugs and to identify new chemical entities as potential therapeutic agents. At the same time, the numbers of distinct neurotransmitters have multiplied. Prior to 1970 only the biogenic amines were well accepted as transmitters. The early 1970s witnessed the gradual acceptance of amino acids as major excitatory and inhibitory neurotransmitters. Identification of opiate receptors and the subsequent identification of the enkephalins as their endogenous ligands led to an appreciation of peptides as putative transmitters and the accumulation of as many as a hundred neuropeptides by the decade's end. In the 1980s the revolutions of molecular biology have been applied aggressively to the neurosciences with molecular cloning for neuropeptide precursors, many important neurochemical enzymes, and receptors for numerous transmitters.

Yet all of this fascinating basic information has been awaiting clinical relevance. Despite our greatly enhanced understanding of brain function,

few if any important new drugs have derived directly from molecular neuroscience research. In psychiatry the major therapeutic agents, the antipsychotics, antidepressants, and antianxiety drugs were all discovered prior to 1965. In neurology, the most widely used anticonvulsants date from more than 40 years ago. L-DOPA, the only major drug developed based on logical thinking from our understanding of neurotransmitters, was introduced into clinical practice in the late 1960s.

This dearth of therapeutic agents based on modern molecular research in brain sciences may soon end, and this book is dedicated to that prospect. Moreover, targets of the potential new generation of therapeutic agents include the most prevalent and disabling diseases of the brain—stroke and neurodegenerative diseases.

Stroke has long been thought to be one of the least promising areas for therapeutic intervention in clinical medicine. Once a blood vessel is occluded, tissue in the area of the blood supply is infarcted. Since neurons in the brain do not regenerate, little could be done for patients beyond physical therapy. In the 1980s thinking in the neurologic community began to change. It was appreciated that neurologic disability following stroke emerges gradually over a period of days and thus could not likely be attributable solely to the initial interruption of blood supply. Quite independently of this line of work, numerous investigators were amassing evidence that besides its role as a physiologic neurotransmitter, glutamate in excess may be toxic. John Olney first provided direct evidence for excitotoxicity elicited by glutamate and its derivatives. The pattern of neuropathology associated with glutamate neurotoxicity resembles very much the pathology of clinical ischemia. Evidence was developed that substantial levels of glutamate accumulate in the extracellular fluid of the brain following cerebral ischemia. The most definitive evidence for a role of glutamate in stroke came from several groups in the late 1980s demonstrating that glutamate receptor antagonists can dramatically prevent neurotoxic damage following interruption of blood flow to the brain. Moreover, some of these agents are neuroprotective when administered after occlusion of cerebral blood vessels. Thus the notion of treating a patient with a glutamate antagonist within a few hours following the stroke emerged in analogy with the highly successful treatment of myocardial infarction using clot-dissolving agents such as tissue plasminogen activator.

Numerous pharmaceutical companies are presently moving toward clinical trials of glutamate antagonists in stroke. Cerebral damage following head trauma, hypoglycemia, and repeated epileptic seizures also is likely to involve excessive glutamate and hence provide therapeutic targets for glutamate antagonists. More indirect evidence hints that major neurodegenerative diseases such as Alzheimer's disease and Huntington's disease involve glutamate neurotoxicity, suggesting similar therapeutic approaches.

While antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors have shown the most promise in therapeutic animal models, blockade of other subtypes of glutamate receptors may also be therapeutic. Moreover, other neuroprotective strategies have been advanced. Adenosine agonists can prevent the release of glutamate. Various compounds related in structure to vitamin E or steroids prevent free radical damage such as lipid peroxidation.

This volume bears witness to the plethora of exciting scientific developments providing the basis for neuroprotective strategies along with a presentation of the major new drug categories that may prove therapeutically effective. Now is an exciting time for those who have waited patiently for the fruits of molecular neuroscience to find application in the major neurologic disabilities of our time.

Preface

PAUL J. MARANGOS AND HARBANS LAL

With the advent of novel chemicals capable of providing protection to the brain cell from injury, a new term has found its way into the neuroscience and neuropharmacology literature: *neuroprotection*. What started with the pioneering studies with excitatory amino acids has now developed into one of the most exciting areas in neuroscience and drug discovery. Moreover, discoveries aimed at neuroprotective treatments may also be extended to treat many neuropathologic conditions involving either the central nervous system or periphery. For the purpose of the present monograph, the term neuroprotection will be limited to strategies designed to protect the central nervous system from any injurious insult. The interest in this field is evident from rapid proliferation of scientific studies being initiated at universities and the pharmaceutical houses alike. In May 1991 the first conference was held on the subject of neuroprotective drugs, and the second international conference on neuroprotective agents was convened in September 1991. The idea of the first book to be published on this topic originated at the May 1991 conference, and some of the contributors to this volume were speakers at that conference.

Brain and spinal cord damage can result from a variety of insults; among them are included stroke, trauma, exposure to neurotoxic environments, hypoxia, surgical insults, hypoglycemia, and neurotoxic drugs. Similarly, the neuroprotection can also be afforded by a variety of agents. For example, NMDA/glutamate antagonists, antioxidants, nerve growth factors, gangliosides, calcium channel blockers, adenosine agonists, neuroleptics, and sphingolipids have been shown to offer protection against brain cell injury in one way or the other. It is now possible to design strategies that can actually slow or prevent the degeneration of nervous tissue in a variety of clinical scenarios including those resulting from acute stroke and head

trauma. Also it may prove possible to employ some of these same approaches to the chronic neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Agents that are effective in this regard are being discovered with great rapidity, and it appears likely that in the next decade a number of these new drugs will be introduced into clinical practice.

What has expedited the clinical revelations is the recent realization that a significant portion of the neural degeneration associated with a number of acute and possibly chronic neurologic diseases actually occurs over a protracted period of time *after* the traumatic event. More importantly the mechanism of neural cell death has also recently been worked out in some detail, and much of it has been found to involve a process referred to as *excitotoxicity*, which seems to cause the majority of tissue damage. It is now clear that various acute and possibly even some of the chronic neurologic diseases result in hyperfunctionality of neurotransmitter systems mostly of the excitatory amino acid (glutamate and aspartate) type. This excitotoxic process results in the excessive stimulation of glutamatergic neurons to the point of metabolic breakdown brought about by excessive intracellular calcium buildup. The toxic process occurs after neural trauma, so it has been further characterized as *delayed excitotoxicity*. This temporal framework provides obvious opportunities for pharmacologic intervention.

The fact that excitatory amino acid (EAA) receptor blockers are neuroprotective in various stroke and head trauma animal models lends further support to the concept and importance of excitotoxicity and to the notion that pharmacologic intervention can be beneficial in both stroke and head trauma. It is therefore now becoming clear that a new class of pharmaceutical agents can now be rationally designed which will prevent much of the tissue damage that ensues in traumatic neurologic disease. As we learn more about the excitotoxic cascade, new drug development strategies are emerging. There has been phenomenal growth in literature on research related to neuroprotection. These relate to discovery of new chemicals, molecular mechanisms, animal models, and novel approaches to establish clinical efficacy. However, these reports are scattered and global overviews in one volume have heretofore been lacking.

The purpose of this volume is to provide such an overview of these emerging new strategies for rational neuroprotective drug design. A number of different approaches have surfaced, ranging from presynaptic modulation which is designed to inhibit the release of glutamate and aspartate (adenosine) to blockade of EAA receptors and the arresting of free radical generation. It is difficult to predict at this time which of these therapeutic interventions will be superior, but it is important to exploit all of them since their usefulness may depend on the clinical situation. The hope of the editors is that this volume will serve to facilitate the interaction between basic, clinical, and pharmaceutical industry researchers and to ultimately speed the process of neuroprotective drug development.

In this volume we have attempted to make a distinction between neuroprotection and neural regeneration. The former refers to strategies that prevent the self-destructive neuronal injury which involves excitotoxicity. Neural regeneration refers to an actual growth of damaged neuronal elements and implies the reestablishment of functional synaptic connections. Herein we only address neuroprotection, as we are planning a future volume on regeneration strategies. It is appropriate to address neuroprotection first since in our view it is somewhat more proximate to the clinic than is regeneration.

This volume will, we hope, be an approachable reference source useful to both clinicians and basic science researchers. The decade of the 1990s will very likely see the introduction of this new class of neuroprotective drugs into the marketplace. As in other areas of medicine there will be an evolution of these agents, with the first ones giving way to more effective second-generation pharmaceuticals. It will indeed be an exciting time for neurologic drug development, especially when one considers the possibility that the drugs developed for the acute disorders (stroke and head trauma) may also be useful in treating the chronic neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

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