New Hopes for Neurologically Disabled

P.N. Tandon

Department of Neurosurgery
All India Institute of Medical Sciences
Neuroscience Centre, New Delhi, India.

The later half of the twentieth century witnessed rapid advances in our understanding of the nervous system, in health and disease, as a result of developments in diverse fields. Beginning in the 1950’s, neurochemical and neuropharmacological investigations resulted in the identification of a host of neurotransmitters, neuromodulators, neurohormones, the mechanisms of their storage, release, reabsorption; their receptors, their preferential neuronal circuits and their role in specific neuronal functions. This led to the development of a number of drugs for both neurological and psychiatric disorders like epilepsy, Parkinson’s disease, depression and schizophrenia. This was followed by emergence of molecular biology as a new discipline which made it possible to explore the neuronal functions at the molecular level. Hundreds of neurotransmitter genes were isolated, cloned and studied in detail. This paved the way for the pharmaceutical industry to develop new drugs to target specific receptors and nerve network, raising hopes for treatment of some of the neurodegenerative disorders. Mental illnesses were no more the exclusive domain of devotees of psychodynamic theories, but were brought under the realm of biological studies.

Molecular mechanisms involved in neuronal damage associated with trauma, ischemia and degeneration were explored in experimental animals. The cascade of secondary changes set in motion by the initial insult were elucidated. The role of glutamate excitotoxicity, NMDA receptors, free radical damage and calcium influx appeared to be a common pathway for progressive damage not only to the neurons but also to oligodendrocytes and consequently the myelin. This prompted search for neuroprotective agents to ameliorate these pathogenetic mechanisms. Calcium channel blockers, free radical scavengers, glutamate antagonists at NMDA and non NMDA receptors, both competitive and non-competitive ones, provided very promising results in experimental studies. For reasons not well understood, these have so far not been found to be useful in clinical practice. Hopefully new strategies will be developed to enhance their therapeutic utility.\(^1\)

Meanwhile, it was discovered that epileptic, hypoglycemic, ischemic and traumatic insults to the nervous system result in inflammatory response which modulates production of neurotrophins like nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin - 3,4,5 and ciliary neurotrophic factor (CNTF) which provide protection against the cascade of events following the insult. The mode of protective action, though not fully understood, is very likely mediated through cytokine IL-1β. Once released, neurotrophic factors can promote enzymatic changes or upregulate certain enzymes, helping in the growth and survival of the neurons, counteracting free radical insult and promoting newer connections. It has now been shown that inflammation also plays a role in the pathogenesis of neurodegeneration. Hence, several neurotrophic factors and even some non-steroidal anti-inflammatory agents have been reported to be beneficial in cases of amyotrophic lateral sclerosis and Alzheimer’s disease.

Recent advances in molecular genetics have ushered in a new era of hope for victims of genetic disorders. The sequencing of human genome has heightened our expectations in this regard. More than 500 genetic diseases are known to affect the nervous system. Genetic basis of more than two dozen diseases has already been identified. As a result of developments in recombinant DNA technology and ability to produce transgenic and gene knock-out animals mimicking human neurological disorders, new insights have been gained about the array of molecules and genes that control the development and functions of the nervous system. Gene mutations and the resulting abnormal proteins responsible for a number of neurodegenerative disorders like Duchenne muscular atrophy, Huntington’s disease, spino celledellar ataxias,
Parkinson’s disease, Alzheimer’s disease etc., have been established. More than a dozen neurological disorders including Fragile X-syndrome, Huntington’s disease, dentatorubral and pallidoluysian atrophy (DRPLA), have been found to be associated with the lengthening (expansion) of tracts of nucleotide triplets such as CTG, CGG and GAA in their genes. While the pathological bases of these diseases vary, repeat expansion is the underlying mutation in all. The pathogenetic mechanism responsible for the neuronal degeneration associated with these repeats is not known. The length of the repeats predicts whether the disease will manifest or not, the age of manifestation and the severity. So far, most of the advances have been made in respect to monogenic disorders but with the availability of human genome data, investigations have begun in respect to polygenic disorders.2

It may be mentioned that, notwithstanding these advances, a cure for a genetic disorder is still not in sight. However application of this knowledge has already helped in detection of carriers, better classification of several disorders and consequently more reliable prediction of prognosis. This brings us to the scope of gene therapy in the management of neurological disorders. It is hoped that gene therapy which is still in its infancy, could be used not only to treat genetic disorders, specially the monogenic ones, but also for control of malignant neoplasia. Thus, for monogenetic recessive disorders the possibility of introduction of a normal or functionally adequate allele of a mutated nuclear gene could provide a ‘gene-replacement’ therapy. In some neurodegenerative disorders like Alzheimer’s or Parkinson’s disease, a therapeutic gene might provide a neurotrophic factor, a neurotransmitter or a cytokine to prevent further degeneration or even reverse the process. It may be mentioned that the first trial to test whether gene therapy can slow progress of Alzheimer’s disease has already been given the go-ahead over a year ago. It is based on the observation that NGF gene therapy could reverse age-related neuronal degeneration in rhesus monkeys, with the genes remaining active for atleast a year. The procedure not only prevents the death of cholinergic neurons but is expected to promote new connections between the cells. Similarly there is already experimental evidence to demonstrate that the growth of malignant gliomas specially glioblastoma can be controlled with the introduction of a ‘suicide gene’ such as thymidine kinase of herpes simplex or a gene that encodes an angiogenesis inhibitory factor. Limited clinical trials have already been permitted. No doubt many technical problems concerning the gene constructs, its delivery, stability, dose, route of injection, efficacy and safety would still need to be standardized in animal models, before being added to the therapeutic armamentarium.

Around 1970s, successful transplantation of fetal neural tissue in rodents and several other species of animals generated new hopes for replacing damaged or lost neural tissue through this approach. The excitement was so great that even before the full implications, specially limitations, could be assessed in animal experiments, a number of overenthusiastic neurosurgeons attempted this procedure, most commonly, for patients with parkinsonism (but also for some others disorders). The feasibility of this approach was soon confirmed, and several hundred such operations were performed around the world. But the experience also brought to light many practical and biological concerns. This led to the search for alternate techniques, whereby immortalized cells, transfected with appropriate genes, grown in culture and cryopreserved, could serve the same purpose. While such efforts were on, two new discoveries i.e. the observations by Fred Gage from California and Peter Eriksson from Goteborg that the mature human brain does spawn neurons atleast at some sites and the isolation of human embryonic stem cells which could be made to differentiate in any desired cell line by Thompson et al opened up a new avenue to harvest cells for neural transplantation. Success has already been achieved in animal models of neurological diseases. These observations made in the last years of the twentieth century have already aroused global interest, and are the subject of intensive investigations in many centres around the world. There are expected to revolutionize the treatment of neurological disorders in the coming decades. 3

We are living in exciting times when it is expected that a variety of new biological approaches - biochemical, molecular and genetic, will hopefully provide new therapies for a large number of currently incurable diseases of the nervous system.4

References