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MOLECULAR AND CELLULAR MECHANISMS OF NEURONAL PLASTICITY IN NORMAL AGING AND ALZHEIMER'S DISEASE

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Preface

The chapters included in this volume are derived from presentations made at the National Institute on Aging Symposium on Molecular and Cellular Mechanisms of Neuronal Plasticity in Aging and Alzheimer's Disease, which was held May 1 through May 3, 1989 in Bethesda, Maryland. The symposium was organized to bring together specialists from many disciplines to discuss issues important for the understanding of the molecular mechanisms underlying plasticity in the nervous system during normal aging and in dementia. Talented neuroscientists, who do not work directly on aging or dementia, were included to provide valuable expertise in research areas not usually considered central to aging or Alzheimer's research. The program was designed to critically analyze mechanisms of neuronal cell death, synaptic plasticity, the role of glia in plasticity, inter- and intracellular molecular signalling, and changes in gene expression and protein processing during aging and dementia. The program was arranged to allow many opportunities for both formal and informal discussion. As a result, many new collaborative research efforts have germinated and we hope future scientific meetings on neuroplasticity will include the fruits of these collaborations.

The symposium was supported by a major gift from the Sigma-Tau Foundation of Rome, Italy, a philanthropic organization dedicated to the advancement and interaction of culture and science. Additional support was received from G.D. Searle and Company, Cortex Pharmaceuticals, Abbott Laboratories, Bristol Myers, and Sterling Drug. The organizers would like to express their gratitude to these sponsors and to T. Franklin Williams, Director, and Zaven Khachaturian, Associate Director, of the National Institute on Aging for their advice and support.

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P. Coleman, G. Higgins and C. Phelps (Eds.)
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CHAPTER 1

Neural plasticity in aging and Alzheimer's disease: some selected comments

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Increasing birth rate and decreasing mortality have led to dramatic increases in the number of older people. It is estimated that the world's elderly population is currently growing at a rate of 2.4%/year from an estimated 290 million over age 65 in 1987 to an anticipated 410 million in the year 2000 (Torrey et al., 1987). The number of "oldest old" (aged 80 and over) is growing even more rapidly. With longer lifespans, diseases associated with old age will become more prevalent. While tremendous advances in the treatment of cancer, heart disease, and stroke have allowed people to live longer, progress has been slower in the treatment of other diseases of later life, particularly brain diseases associated with aging. Among these diseases, the dementias present a particularly difficult research problem, one which many neuroscientists are actively investigating.

Neural plasticity can be defined as adaptive changes in structure and function of the nervous system occurring during all stages of development, as a result of experience, or following injury. Many levels of complexity have been attached to the concept of plasticity with time spans ranging from seconds to years; from very precise modifications in behavior related to learning and memory to global responses such as attempts to recover function following environmental insult. The immature central nervous system (CNS) is considered to be extremely plastic but, until recently, the mature and aging CNS were thought to have very little plastic capability. We now know axonal sprouting, dendritic growth, and glial changes occur in older animal and human brains.

The most consistent changes described in normally aging brain are decreased brain weight accompanied by cortical atrophy, loss of cortical neurons, accumulation of lipofuscin storage granules in neurons and glia, and hypertrophic changes in neuroglia (Landfield, 1982). Neuron loss in non-cortical areas is less consistent with some brain stem nuclei showing significant reductions in cell numbers while others appear normal (reviewed in Coleman and Flood, 1987). Earlier work described decreased neuronal density with age in several cortical areas (Brody, 1970), but more recent studies indicate that the losses may not be as great as the earlier work indicated. While the number of large neurons decreases, smaller neurons are more numerous. This suggests that the changes previously reported may be due partially to shrinkage of the large cells (Terry et al., 1987). With glial cell density also increasing, the overall decrease in cortical volume probably results from both cell loss and reduction in volume of cells and neurites. It is important to discover the molecular mechanisms underlying the processes of cell shrinkage and cell death in normal aging.

Reports on changes in dendritic extent with advancing age depend on the area of brain examined, and the method of tissue preparation. Using the rapid Golgi technique, Scheibel et al. (1975)

reported losses of dendrites and dendritic spines in pyramidal cells of the frontal and temporal lobe neocortex and hippocampus while Coleman's group (Buell and Coleman, 1979) using the Golgi – Cox method, described increased dendritic branching and growth in pyramidal cells of the parahippocampal gyrus and suggested that dendritic growth may be an attempt to compensate for loss of neighboring neurons. A larger dendritic surface area would provide new synaptic sites for afferent axons formerly connected to the now missing cells. However, in the very old, Flood et al. (1985) found that there was regression of dendritic extent in pyramidal cells of the dentate gyrus while in still other areas of the hippocampus, dendritic extent in pyramidal cells was unchanged. Thus even in the so-called plastic areas of the brain, dendritic changes with aging are variable.

Cotman and his group (reviewed in Cotman and Anderson, 1988) have investigated reactive synaptogenesis in the aging brain and determined that hippocampal afferent axons in the brains of aged rodents demonstrate a remarkable capacity for sprouting and synaptogenesis although the response may not be as rapid as in younger animals (Scheff et al., 1980). Synaptic regrowth is slower and less complete in older animals. Whether the reconnection is adaptive remains to be demonstrated.

Neuroglia, astrocytes in particular, play a dynamic role in brain function by modulating the extraneuronal microenvironment. Astrocytes have specific receptors for neurotransmitters and a complement of enzyme systems which aid in the processing of neurotransmitters and metabolites released during neuronal activity. These cells are exquisitely sensitive to changes in the brain environment and, after injury to the central nervous system, demonstrate dramatic reactive properties. Very few studies of physiological properties of aging astrocytes have been conducted. However, beginning in middle age and increasing into old age, marked astrocyte hypertrophy occurs in the vicinity of terminal synaptic fields in the hippocampus (Lindsey et al., 1979). This results in increased glial volume but not number. Other studies have noted increases in the glial – neuronal ratio and glial reactivity with advancing age in a number of species including man (Hansen et al., 1987).

Because memory loss is a hallmark of Alzheimer's disease, much attention has been focused on the physiological basis of memory and the changes that occur during aging. Basic understanding of memory decline (reduced plasticity) in normal aging may provide insight into memory losses in dementia. There is convincing evidence that aging leads to impairment of tasks requiring behavioral plasticity (reviewed in Landfield et al., 1986). This impairment relates primarily to recall of recent events and includes faster rates of forgetting. Studies of the granule cells in the hippocampus of younger animals show an activity-dependent long-term enhancement (LTE) or potentiation (LTP) of synaptic strength that may represent a mechanism for information storage. This stimulation-induced effect shows some evidence of decline in older animals (Sharp et al., 1987; Barnes, this volume).

Dementia is a clinical state characterized by the development of memory and learning impairments, loss of intellectual and cognitive functions, and disorientation (Katzman, 1986). This complex of symptoms can be caused by a number of disorders, but the most common cause of dementia is Alzheimer's disease accounting for 60 – 70% of all cases.

It was in 1907 that Alois Alzheimer published the first case report, "about a peculiar disease of the cerebral cortex" (Alzheimer, 1907). He described a 51-year-old patient whose ability to encode information was severely disturbed and had compromised language functions. At autopsy the brain was atrophic and demonstrated "abnormal accumulations of neurofibrillary bundles", "miliary foci" (neuritic plaques) and "deposits of a peculiar substance" (amyloid) in the cerebral cortex. There was also cell loss in the upper layers of the cerebral cortex accompanied by changes in glia. These findings have been confirmed and studied more intensely in many cases of dementia

of the Alzheimer type.

Estimates vary for the prevalence of Alzheimer's disease in the U.S. but recent studies indicate that as many as 4 million Americans are afflicted. Since the primary risk factor is age, by the year 2040 the prevalence of dementia is expected to be as much as 5 times greater if significant progress is not made in treatment or prevention.

In order to understand the changes that occur in the brains of demented patients, it is first necessary to distinguish them from changes occurring in the brain during normal aging in disease-free individuals and from changes seen in other brain diseases not related to dementia. The pathological changes in Alzheimer's disease appear to be particularly severe in those areas of the brain that are considered to be plastic including areas closely associated with cognitive processing such as the hippocampus, amygdala, and other limbic structures as well as the neocortical association areas. Basal forebrain and brain stem neurons are also affected. The cognitive deficits associated with the dementias stem from dysfunction of these brain areas and, therefore, much of the research on dementias focuses on structure and function of these plastic areas, particularly the hippocampus and the neocortex. Study of these areas in nondemented individuals and in experimental animals has contributed valuable information about synaptic plasticity and its relation to learning and memory during normal aging (See Barnes, this volume).

When the disease process is superimposed on the aging process, cortical atrophy, cell loss and proliferation of neuroglia are even more pronounced than with aging alone. Similar histological changes exist in normal and Alzheimer's brains but differ in degree. In very old patients and in late onset disease differences are particularly difficult to identify; this may explain why neurochemical differences between age-matched controls and Alzheimer's subjects are not always obvious (Hauw et al., 1988). An important finding in AD brains is specific loss of cells in association areas of the neocortex, limbic structures, nucleus basalis, and locus coeruleus accompanied by reductions in levels of neurotransmitters including acetylcholine, serotonin, norepinephrine, GABA (gamma-aminobutyric acid), aspartate, and corticotrophin releasing factor. Transmitter reductions stem from dysfunction or death of specific cell types. For example the reduction of acetylcholine is closely correlated with the shrinkage and loss of cholinergic cells in nucleus basalis and reduction of norepinephrine reflects loss of cells in the nucleus of the locus coeruleus. It is not yet clear which transmitter(s) are associated with the specific cells lost in the neocortex although glutamate is a prime candidate.

The molecular mechanisms underlying selective cell death are under study in a number of different laboratories. Some forms of neuronal cell death result from a cascade of events set in motion by stimulation of receptors on the cell membrane leading to abnormal phosphorylation of proteins. The details of these events are still not known but it is thought that changes in calcium homeostasis, gene expression and protein processing lead to dysfunction and eventual cell death. One class of receptor implicated in cell death is the NMDA receptor which is normally stimulated by excitatory amino acids such as glutamate. However, under certain circumstances excitatory amino acids or other endogenous factors can be excitotoxic, causing overstimulation of the receptors and activation of the events leading to cell death (see Olney, this volume). Receptor and channel blockers or other compounds that might interrupt the subsequent cascade of events leading to cell death may serve to protect vulnerable cells. These compounds would need to be delivered to the appropriate cells while not interfering with normal cell function. Among the compounds being considered are the calcium channel blocker, nimodipine, and NMDA receptor blockers. If vulnerable cells can be protected, the progress of Alzheimer's disease might be slowed.

The role of neurotrophic factors in the normal aging brain and in Alzheimer's disease is a topic of great interest. Nerve growth factor (NGF) is the