Glial Cells in Aging and Neurodegeneration.
A Satellite Symposium to the 28th Annual Meeting of the Society for Neuroscience.
Los Angeles, CA, November 7, 1998

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The Satellite Symposium “Glial cells in Aging and Neurodegeneration” was organized by The National Institute of Aging (NIA) and held in the Los Angeles Convention Hall on Saturday, November 7, 1998. It consisted of six lectures by distinguished scientists from leading American Universities, whose research was supported by NIA.

A. Peters (Boston Univ., Boston, MA) discussed the effects of aging on primate neuroglial cells. He attempted to correlate aging-induced anatomical damage with the behavior of Rhesus monkeys. He correlated degeneration of neurons in the cortical area 46 with the performance of animals in the delayed non-matching to sample task. The decrease in cortical thickness accompanied the loss of synapses and astrocytosis. The astrocytic processes thickened and the number of astroglial filaments increased. The perikarya and processes in oligodendroglia were also affected by age; they developed dense inclusion bodies and myelin sheaths deteriorated. The breakdown of myelin correlated with age and behavioral changes in monkeys. Peters suggested that cognitive decline is caused by myelin breakdown and consequent disruption of neuronal circuits.

C. W. Cotman et al. (Inst. Brain Aging and Dementia, Univ. CA, Irvine, CA) studied reactive gliosis in Alzheimer’s disease (AD) and in frontotemporal dementia (FTD). Reactive astrogliosis is commonly found in the brain of patients with AD. Cotman and his associates found that β-amyloid fibrils induce reactive astrogliosis in primary cell cultures and increase expression of basic fibroblast growth factor, interleukin-1β and glutamine synthetase. β-Amyloid fibrils can also cause cell death or inflammatory reactions in cultured microglia. Microglial apoptosis is known to occur in the brain of patients with AD. In FTD, the glial activation process is different from that in patients with AD. The main finding in the brain of patients with FTD is the apoptotic cell death of astrocytes with severe astrogliosis in the subcortical white matter. Active caspase-3 is found in soma and processes of degenerated astrocytes. The levels of glutamate transporter are decreased. Abnormal functioning of astrocytes is likely to affect neurons. Glial activation in AD as well as in FTD is likely to influence the disease process.

W. S. T. Griffin et al. (Univ. Arkansas Medical School, Little Rock, AR) reviewed the role of the cytokine cycle in the pathogenesis of AD. According to this group, the
overexpression of IL-1 initiates cytokine cycle that may be beneficial initially but harmful in the long term. IL-1 promotes processing of β-amyloid processing protein (β-APP) and activates astroglia. Activation of astrocytes is likely to enhance the formation of S100β, which increases not only the synthesis of APP, but also intraneuronal Ca²⁺. The resulting neuronal injury increases IL-1 expression further and, therefore, promotes the cytokine cycle.

G. M. Pasinetti (Mount Sinai School of Medicine, New York, NY) reviewed the role of neuronal cyclooxygenase (COX-2) expression in glial activity and neurodegeneration. The hypothesis that neuronal COX-2 expression contributes to the neuronal damage in AD is supported by findings that activated neuroglia surround plaques in the brain of patients with AD and that microglial accumulation is reduced in patients treated with non-steroidal antinflammatory drugs with cyclooxygenase inhibitory activity. Pasinetti demonstrated that COX-2 is upregulated in the cortex of patients with AD and that it correlates with the deposition of amyloid plaques. He generated a transgenic mouse model that overexpresses human COX-2 and found that in this model there is an increase in β-APP-induced neurodegeneration. These mice are also more susceptible to excitotoxic lesions and exhibit an age-dependent accumulation of microglia. Pasinetti suggested that microglial response could be mediated by COX-generated prostanoids and controlled by COX-2 inhibitors.

J. D. Rothstein (Johns Hopkins Univ., Baltimore, MD) discussed aberrant RNA processing as a glial basis for neurodegeneration. The glutamate transporter protein (EAAT2) that is selective for astrocytes is lost in amyotrophic lateral sclerosis (ALS) as well as in transgenic models of hereditary disease of motor neurons. The loss of EAAT2 in ALS is attributed to the formation of truncated EAAT2 RNA species. The aberrant processing or metabolism of RNA is likely to be involved in the pathogenesis of neurodegenerative diseases.

M. P. Goldberg (Washington Univ. School of Medicine, St. Louis, MO) suggested that glial excitotoxicity may be involved in the pathogenesis of many neurodegenerative diseases of the central nervous system. He studied astrocytes and oligodendrocytes from mouse cerebral hemispheres in primary cultures and found that they express AMPA/kainate but not N-methyl-D-aspartate (NMDA) receptors. In type-1 astrocytes NMDA receptors are rapidly desensitized, so that they are not likely to be injured by glutamate agonists. Oligodendrocytes are, however, highly sensitive to the activation of glutamate receptors. Some AMPA antagonists protect oligodendrocytes from damage due to transient oxygen-glucose deprivation. Glutamate-induced damage of oligodendrocytes is likely to contribute to the white matter injury in stroke, head trauma and various neurodegenerative diseases.