Alzheimer's and Related Diseases Research Award Fund

FINAL PROJECT REPORTS FROM THE 1997-1998 ALZHEIMER'S RESEARCH AWARD FUND

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 to stimulate innovative investigations into Alzheimer's Disease along a variety of avenues, such as the causes, diagnosis, and treatment of the disorder; public policy and financing of care; and the social and psychological impacts of the disease upon the individual, family and community. The ARDRAF competition for these pilot study funds ($16,500) is administered by the Virginia Center on Aging at Virginia Commonwealth University in Richmond.

UVAThomas C. Foster, Ph.D., Department of Psychology, "Mechanism for Memory Impairment and Pathophysiology Associated with Aging and Alzheimer's Disease"

Calcium is involved in the signal transmission between nerve cells. In turn, the transmission of information between these cells is required for memory. There is ample evidence for disruption of calcium regulation in aging and age-associated neuropathologies such as Alzheimer's disease. Our work indicates that changes in the calcium-dependent processes for neuronal signaling are altered during aging and are associated with memory impairments similar to those observed early in the clinical course of the disease.

Using aging rats as a model, our research indicates that changes in the electrical transmission properties of the brain and age-related impairments in memory can be reversed by treatments that block calcium entry into brain cells. This raises the possibility that future pharmacological interventions might be devised to act on calcium dependent processes for the prevention or treatment of age-associated neurological disorders.

EVMSEvan T. Keller, D.V.M., Ph.D., Glennan Center for Aging, and Paul F. Aravich, Ph.D., Department of Anatomy and Neurobiology, "Do Free Radicals Induce Interleukin-6 Expression in the Rat Hippocampus? A Model for Alzheimer's Disease"

Alzheimer's disease (AD) is a progressive degeneration of the brain that leads to dementia and death. The cause of AD is unknown, but levels of a protein called interleukin-6 (IL-6) are elevated in the brains of patients with AD. Because IL-6 both stimulates inflammation and increases production of the amyloid protein associated with AD, it may play a key role in the development of AD. The cause of high IL-6 levels in the brain, in turn, is unknown, but chemical substances called free radicals may contribute to this. Free radicals are chemicals that damage fats, proteins and genes. They increase with age and increase IL-6 levels in many different tissues. Free radicals are elevated in the brains of AD patients and may also contribute to the development of AD.

We believe that free radicals contribute to the development of AD by increasing IL-6 levels in the brain. To examine this possibility, we treated rats with high levels of oxygen to increase free radical activity in their brains. We then measured IL-6 protein levels in the hippocampal region of the brain. We found that IL-6 levels were increased by free radicals in the hippocampus. This information suggests that inhibiting IL-6 production in the brain may prevent or slow the development of AD.

EVMSFrancis J. Liuzzi, Ph.D., Department of Anatomy and Neurobiology, "Does Estrogen Protect Basal Forebrain Neurons from Neurodegenerative Changes?"

There is growing scientific evidence that estrogen plays an important role in brain development. The evidence suggests that neurons of the basal forebrain, a region implicated in memory and learning, may depend on estrogen during development. More recent data, from a number of laboratories, suggest that the dependence of basal forebrain neurons on estrogen may extend into adulthood. In humans, degenerative changes in these neurons have been implicated in Alzheimer's disease. Interestingly, in a small group of women Alzheimer's patients, estrogen replacement improved cognitive function.

In our laboratory, we have used ovariectomized adult female rats as a model of menopause. Removal of the ovaries depletes virtually all estrogen in the body. We had shown, in the sensory neurons of these animals, that estrogen had dramatic effects on one neuronal gene in particular, the neurofilament gene. This gene is essential for the maintenance of the neuron's cell body and processes. If the expression of this gene decreases, the neurons and their processes shrink and they become non-functional.

In the ARDRAF funded research in our laboratory, we examined the effects of estrogen replacement on basal forebrain neuronal expression of the neurofilament gene. We expected that a loss of estrogen would cause a decrease in the expression of this gene in basal forebrain neurons and their consequent shrinkage. We found, however, no difference in neurofilament gene expression between the untreated and the estrogen replaced animals. Our data suggest that basal forebrain neuronal neurofilament gene expression is <u>not</u> dependent on estrogen alone and that loss of other factors, such as nerve growth factor, in combination with a loss of estrogen, may play a role in the decline of basal forebrain neurons.

UVARussell H. Swerdlow, M.D., Dept. of Neurology, UVA Health Sciences Center, "Cytochrome Oxidase Associated Pathophysiology in Alzheimer's Disease"

Work funded by the Alzheimer's and Related Disease Research Award Fund of the Commonwealth of Virginia now provides insight into altered cell functioning in Alzheimer's disease. This research helps scientists understand why brain cells degenerate in this disease, and may also apply to other related diseases of the aged nervous system, such as Parkinson's disease and amyotrophic lateral sclerosis (Lou Gehrig's disease).

This work explored the status of mitochondria in Alzheimer's disease patients. Mitochondria are important components of most cells of the body and are responsible for cell respiration and energy generation. For over a decade, scientists knew that mitochondria were abnormal in persons with Alzheimer's disease, but were not sure why. This research indicates that at least some degree of mitochondrial dysfunction in Alzheimer's disease is related to disruption of specific genes located within the mitochondria proper. These genes carry the blueprints for constructing an important cell respiration enzyme called cytochrome oxidase.

Although it is not yet clear why these mitochondrial genes are disrupted, the consequences are profound. In addition to diminished functioning of cytochrome oxidase, mitochondria in Alzheimer's patients appear to act as free radical generators and disrupt communication switchboards within cells. Because of this, cells become fragile and die when provoked in ways that healthy cells easily tolerate.

On an optimistic note, some of this work demonstrates that, under experimental conditions, certain compounds can help limit the damage caused by mitochondrial dysfunction. This suggests that the development of drugs that act upon mitochondria may one day prove useful in the treatment of Alzheimer's disease.