INSULIN RESISTANCE AND AGING NEUROLOGICAL COMPLICATIONS AND CONSEQUENCES

Larry Reagan (P)

Department of Pharmacology, Physiology and Neuroscience, University of South Carolina School of Medicine, Columbia, SC 29208, USA

The hippocampus is an important integration center for learning and memory in the mammalian central nervous system (CNS) and is particularly sensitive and responsive to changes in insulin and glucose concentrations. Indeed, insulin or glucose administration improves cognitive performance in a variety of settings, including aging and diabetes phenotypes. Conversely, insulin resistance and obesity adversely affect brain structure and function and may contribute to the development and progression of neurological disorders such as depression, dementia and Alzheimer's disease. Our previous studies demonstrated that increases in allostatic load associated with hyperglycemia produce behavioral, neuroanatomical and neurochemical changes in the adult rat hippocampus, neurological changes that are suggestive of accelerated brain aging. While additional factors, such as cerebrovascular changes and increases in oxidative stress are involved in these processes, the role of the insulin receptor (IR) system has come under greater scrutiny in the development of age and diabetes-related neurological complications. Unlike peripheral tissues, much less is known regarding the activation of IR system in the CNS. Accordingly, our recent studies have utilized a variety of cellular and molecular approaches to determine the signal transduction mechanisms utilized by neuronal IRs and how activation of these pathways may mediate the central actions of insulin. Analysis of IR signaling using *in vitro* and *in vivo* approaches suggest that the neuronal IRs may activate similar signal transduction pathways as described in peripheral tissues. Design of viral vectors to target IR expression in region-specific manner has provided additional information regarding the actions of the central IR system. These novel experimental approaches provide insight into the signaling mechanisms utilized by neuronal IRs and ultimately will allow for examination of the contribution of the IR system upon the neuronal consequences of diabetes and aging