Association Monégasque pour la Recherche sur la Maladie d'Alzheimer
AMPA

1st International Congress on Alzheimer's Disease and Advanced Neurotechnologies

NEUROVIGIL

Title: Diabetes-A Strong Risk Factor for Cognitive Dysfunction and Alzheimer's Disease

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In addition to the well-known complications of type 1 (T1D) and type 2 (T2D) diabetes such as heart disease, stroke and kidney failure, cognitive dysfunction and Alzheimer's disease (AD) are emerging as serious consequences of diabetes. Studies have shown that diabetes duration is a particularly important risk factor for the development of AD, consistent with the idea that the physiological alterations associated with diabetes that develop over the course of the disease may play an important role in the loss of cognitive function. Even more troubling are the observations that the changes that precede overt diabetes such as hyperinsulinemia and hyperglycemia are also associated with an increased risk of cognitive dysfunction and AD. Thus, with 1.6 million new cases of diabetes being diagnosed in persons aged 20 years or older each year and 2 million adolescents aged 12-19 years exhibiting pre-diabetes, the number of Americans developing AD has the potential to increase to epidemic proportions, well above the current 1 in 10 Americans over the age of 65 years diagnosed with AD. Many of the metabolic changes associated with diabetes such as oxidative stress, alterations in glucose and fatty acid metabolism, inflammation and the accumulation of oxidatively modified and glycated proteins are also associated with AD. In addition, both insulin resistance and hyperinsulinemia can alter insulin signaling in the brain which may contribute to the impact of T2D on cognitive function and development of AD. In support of these observations, using a transgenic mouse model of AD, we recently showed that diabetes can greatly accelerate the development of AD-associated changes in the brain. Since there are multiple mechanisms that are implicated in the age- and diabetes-related decline in cognitive function, it is unlikely that drugs with only a single target will be effective at slowing the onset of AD. A better approach is to identify small molecules that have multiple biological activities associated with both the maintenance of cognitive function and the prevention of diabetic complications. Over the last few years, we have identified an orally active, novel neuroprotective and cognition-enhancing molecule, the flavonoid fisetin. Recently we showed that fisetin is also effective against several complications of diabetes. In addition, fisetin can prevent the loss of learning and memory seen in a transgenic mouse model of AD. These results suggest that fisetin has the ability to reduce the brain-associated complications of diabetes including AD, and provide additional support to the data suggesting that at least some of the molecular pathways leading to the pathological changes in both diseases are shared.