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Amylin: What might be its role in Alzheimer's disease and how could this affect therapy?

Charles De Carli
University of California, USA

Amylin, an amyloidogenic hormone synthesized and co-secreted with insulin by pancreatic B-cells, has binding sites in the brain possibly regulating satiety and gastric emptying. It is elevated in obesity and pre-diabetic insulin resistance (hyperamylinemia) leading to amylin amyloid deposition in the pancreas. Moreover, amylin deposition in pancreatic islets is an important source of oxidative and inflammatory stress leading to atrophy of pancreatic islets and development of type 2 diabetes (T2D). One possible mechanism of amylin accumulation in peripheral organs is through deposition of circulating amylin oligomers, which were found in both blood vessels and parenchyma of kidneys, heart and - as we have recently shown - brain. Hence, amylin amyloid infiltration in the brain may be an important contributor to cerebrovascular injury and neurodegeneration observed in demented humans. Treatment of hyperamylinemia or the consequent formation of circulating amylin oligomers, therefore, could be a feasible therapeutic target to protect the aging brain or slow neurodegenerative processes. Numerous epidemiological studies show significant associations between presumed T2D and risk for Alzheimer's disease (AD). This increased risk extends to both obesity, the major risk factor for insulin resistance, and T2D. Pathological studies indicate that dementia risk associated with T2D is independent of Alzheimer's pathology and suggest that the increased dementia risk is likely due to vascular brain injury. An independent study also showed increased AD pathology in T2D. Brain imaging studies, however, demonstrate that the risk associated with dementia and T2D is independent of vascular disease. At least one study found significant hippocampal atrophy suggesting that the association between diabetes and AD may involve shared pathophysiological processes. Recent reviews point to possible pathological pathways whereby hyperinsulinemia may lead to increased AD pathology through altered cerebral clearance of amyloid b protein and hyperphosphorylation. As hypothesized by de la Monte, peripheral hyperinsulinemia is associated with impairments in cerebral glucose utilization through brain insulin and IGF resistance. Impaired insulin and IGF signalling lead to increased amyloid precursor protein expression increased amyloid b production and hyperphosphorylation of microtubule t protein, which are the two hallmark pathologic features of AD. Similarly, increased insulin levels in the brain may saturate the brain insulin degrading enzyme system or reduce LRP-1 levels which are also mechanisms for amyloid b clearance.

Biography

Charles De Carli, MD, is Professor of Neurology at the University of California in Davis, California. He is the Director of the Alzheimer's disease center, a United States National Institutes of Health funded Alzheimer's Research Center. He is also Director of the Imaging of Dementia and Aging (IDeA) laboratory. His research focuses on using advanced structural and functional brain imaging to study normal aging, mild cognitive impairment and dementia and the role of genetics, cerebrovascular and Alzheimer's disease on these processes. He is a recipient of the J. Allyn Taylor International Prize in Medicine-Imaging of the Aging Brain in recognition of his work. In addition, he is the Editor-in-Chief of Alzheimer Disease and Associated Disorders, an international journal of AD research.

cdecarli@ucdavis.edu