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HDAC IIa-specific inhibitors as a potential novel therapy for type 2 diabetes-mediated cognitive deterioration in alzheimer's disease

Giulio Maria Pasinetti

Mount Sinai School of Medicine, USA

Abstract

Our laboratory recently demonstrated that epigenetic chromatin modifications associated with type-2 diabetes (T2DM) may play a role in brain pathophysiology in neurodegenerative disorders. We previously discovered that there are significant changes in the expression of select chromatin modification enzymes, such as histone deacetylases (HDACs), in the brains of T2DM subjects compared to control subjects, and that these changes coincide with altered expression of proteins involved in synaptic function, such as PSD95 and synaptophysin. We hypothesized that T2DM may induce epigenetic modifications associated with increased susceptibility to Alzheimer's disease (AD)-type neurodegeneration. Using a mouse model of diet-induced T2DM, we found that, similar to humans, T2DM mice showed differential expression of epigenetic-modifying enzymes in the brain compared to controls. In particular, we found significant up-regulation of HDAC class IIa, including HDACs 4, 5, and 9, in the brains of diabetic mice. These alterations coincided with increased susceptibility to oligomeric Aβ (oAβ) induced synaptic toxicity and oAβ-induced synaptic dysfunction, as assessed by long term potentiation (LTP). Most interestingly, we found that inhibition of class IIa HDACs using an HDAC IIa-specific inhibitor, MC1568, increased transcription levels of PSD95 and synaptophysin in primary neuron cultures from C57Bl6/J mice and prevented LTP deficits found in old-T2DM mouse ex vivo hippocampal slices. The studies provide much-needed information regarding mechanisms underlying potential risks posed by diabetes in terms of diminishing cognitive function and may provide the basis for strategies aimed at early primary prevention against key risk factors for AD.

Biography

Giulio Maria Pasinetti's research on lifestyle factors and metabolic co-morbidities influencing clinical dementia, neurodegeneration and Alzheimer's disease has made him a top expert in his field. He has received over 30 grants and published over 160 groundbreaking research articles. Dr. Pasinetti is a Professor of Neurology, Psychiatry, Neuroscience, and Geriatrics and Adult Development, and is Director of the Brain Institute Center of Excellence for Novel Approaches to Neurotherapeutics at Mount Sinai School of Medicine. He also serves as Director of the Basic and Biomedical Research and Training, Geriatric Education and Clinical Center at the Bronx Veterans Affairs Medical Center.