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Neuro-Epigenetic Changes on Diabetes Induced-Synaptic Fidelity in Brain

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Abstract : Background and Aim: Epigenetics are the inaudible signatures of several pathological processes in the brain. This study understands the influence of DNA methylation, a major epigenetic modification, in the prefrontal cortex and hippocampus of the diabetic brain and its notable effect on the cellular chaperones and synaptic proteins. Method: Chronic high fat diet and STZ-induced diabetic mice were studied for cognitive dysfunction, and global DNA methylation, as well as DNA methyltransferase (DNMT) activity, were assessed. Further, the cellular chaperones and synaptic proteins were examined using DNMT inhibitor, 5-aza-2′-deoxycytidine (5-aza-dC)-via intracerebroventricular injection. Moreover, % methylation of these synaptic proteins were also studied so as to correlate its epigenetic involvement. Computationally, its interaction with the DNMT enzyme were also studied using bioinformatic tools. Histological studies for morphological alterations and neuronal degeneration were also studied. Neurogenesis, a characteristic marker for new learning and memory formation, was also assessed via the BrdU staining. Finally, the most important behavioral studies, including the Morris water maze, Y maze, passive avoidance, and Novel object recognition test, were performed to study its cognitive functions. Results: Altered global DNA methylation and increased levels of DNMTs within the nucleus were confirmed in the cortex and hippocampus of the diseased mice, suggesting hypermethylation at a genetic level. Treatment with AzadC, a global DNA demethylating agent, ameliorated the protein and gene expression of the cellular chaperones and synaptic fidelity. Furthermore, the methylation analysis profile showed hypermethylation of the hsf1 protein, a master regulator for chaperones and thus, confirmed the epigenetic involvement in the diseased brain. Morphological improvements and decreased neurodegeneration, along with enhanced neurogenesis in the treatment group, suggest that epigenetic modulations do participate in learning and memory. This is supported by the improved behavioral test battery seen in the treatment group. Conclusion: DNA methylation could possibly accord in dysregulating the memory-associated proteins at chronic stages in type 2 diabetes. This could suggest a substantial contribution to the underlying pathophysiology of several metabolic syndromes like insulin resistance, obesity and also participate in transitioning this damage centrally, such as cognitive dysfunction.

Keywords : epigenetics, cognition, chaperones, DNA methylation
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