Intranasal insulin delivery is protective against diabetes mellitus-related brain atrophy and white matter abnormalities in experimental diabetes mellitus

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Background: Longstanding diabetes mellitus (DM) has been associated with childhood and adult cognitive impairment, as well as dementia. In human diabetic patients, magnetic resonance imaging (MRI) of the brain identifies whole brain atrophy and white matter abnormalities. However, the mechanisms leading to brain dysfunction in DM remain poorly understood.

Methods: We studied a long term model of DM (streptozotocin-induced) in mice along with littermate controls. After 3 months of DM, both diabetic and control mice were treated with daily intranasal insulin (0.87 U/day) or saline over the next 5 months (8 months of DM total). Blood glucose testing and cognitive testing was performed weekly after 3 months of DM. After 8 months of DM, magnetic resonance imaging (MRI) of the brain was performed in anesthetized mice using a 9.4T MR system. T1, T2, and perfusion maps were acquired using inversion recovery Snapshot FLASH, spin echo multi-echo and arterial spin tagging imaging sequences, respectively. Images were acquired using a FOV=2cmx2cm, slice thickness of 0.75 mm and matrix size of 256x128. Immediately following MRI, brain harvesting was performed and brains were weighed and preserved for morphological studies.

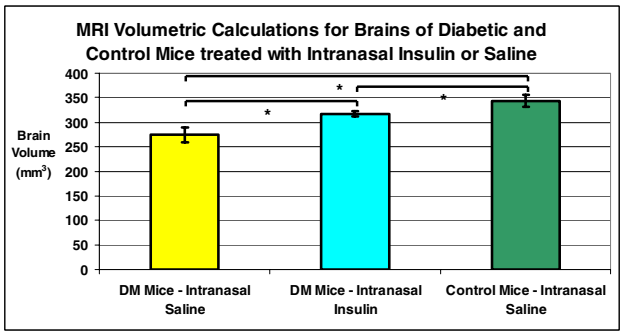

Figure 1 – Volumetric Analysis of DM and control mouse brains

Results: Intranasal insulin tagged with a fluorescent marker was identified within brain regions 6 hours after delivery. Cognitive behavioural testing (Holeboard, Radial Arm, and Morris Water Maze tests) identified the development of loss of learned visuospatial functioning in diabetic mice after 6-7 months of DM, with definite preservation of cognitive function in intranasal insulin-treated mice. Intranasal insulin was also associated with less DM-related mortality. There was no significant change in blood glucose found with intranasal insulin delivery. Volumetric assessment of brains identified brain atrophy in DM mice and brain mass was also lost in DM mice, with preservation of brain volume and mass identified in intranasal insulin-treated DM mice (Figure 1). As noted previously, T2 map values were generally depressed in DM mice, although specific focal heightened T2 values were detected in DM mice hippocampi. There was no difference in T2 values nor presence of T2 hyperintensities between intranasal insulin and saline treated DM mice. Perfusion-weighted imaging demonstrated no difference in tissue blood flow in subcortical structures between DM and control mice, although DM mice cortices had significantly increased perfusion values without relationship to intranasal delivery (Figures 2,3).

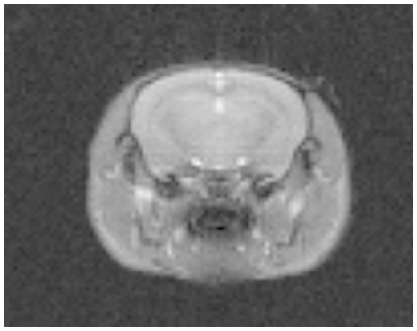

Figure 2 – An example of a perfusion weighted image of a DM mouse brain

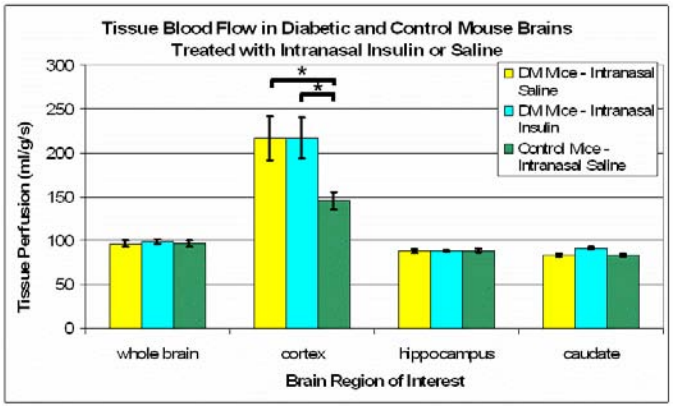

Figure 3 – Perfusion weighted imaging of DM and control mouse brains

Conclusion: Delivery of small amounts of insulin through an intranasal route prevents the development of cognitive decline and brain atrophy associated with experimental DM without any effect upon blood glucose levels. It is unlikely that tissue perfusion abnormalities are contributing to the identified abnormalities in the experimental DM brain. Further studies are needed to understand the protective effect of insulin and the pathophysiology of cognitive changes, white matter abnormalities, and brain atrophy in both experimental and human DM.