Role of Glucose and Insulin on Mitochondrial Health in Mouse Hippocampal Cells

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Abstract

Alzheimer’s disease (AD), is a progressive neurodegenerative disease associated with cognitive decline, dementia, and eventual death. AD cases are increasing with an estimated global prevalence of about 80 million predicted by 2040. Therefore, finding early stage prevention or treatment options are important. Besides aging, studies have identified Type 2 Diabetes (T2D) as a risk factor for developing dementia attributable to AD. Though the effects of T2D on AD progression are known, the possibility of glucose or insulin having independent or concurrent roles in AD progression have not been answered. Mitochondrial dysfunction is a strong contributor of AD pathology and identifying factors involved might provide therapeutic options.

Here we investigated the effect of high glucose or high insulin on mitochondrial health in mouse hippocampal cells (HT-22). The hippocampus is the region of the brain for long-term memory therefore, the objective was to examine effect of high glucose and/or insulin on the genes and proteins involved in mitochondrial function, fusion and biogenesis. Cells were treated with 50 mM glucose or 100 nM insulin for 24 hours. Further, to determine the combined effect of high glucose and insulin, cells were also treated with 50 mM glucose and 100 nM insulin for 24 hours. Following treatment, cells were collected and processed for gene expression and protein expression analysis.

Synopsis gene (PSD95) involved in synaptic function between neurons and genes related to mitochondrial dynamics, including fusion (Fis1 and Drp1), fusion (Mfn1), and biogenesis (Opa1) were found to be downregulated with glucose and a combined insulin-glucose challenge, whereas insulin challenge showed increased expression of fusion-related genes.

In neuronal cells, it appears that glucose and insulin possibly affect mitochondrial function differently leading to cognitive impairment and AD pathology. However, additional research is needed in vivo to determine their effect.

Methods

Undifferentiated HT-22 mouse hippocampal cells were grown in regular growth media supplemented with 27.5 mM glucose and 100 nm insulin for 24 hours, following which cells were exposed to media supplemented with a final concentration of 50 mM glucose and 100 nm insulin for an additional 24 hours.

Results

In neuronal cells, it appears that glucose and insulin possibly affect mitochondrial function differently leading to cognitive impairment and AD pathology. However, additional research is needed in vivo to determine their effect.

Conclusions

In 24-hour 27.5 mM glucose and 100 nM insulin challenge:

- DRP1 (mitochondrial fission gene) were found to be significantly downregulated.
- PSD95 (synaptic plasticity gene) OPA1 (mitochondrial biogenesis gene) and MFN1 (mitochondrial fusion gene) were found to be significantly downregulated with glucose and a combined insulin-glucose challenge.
- Insulin challenge showed significant increased expression of fusion-related gene DRP1.

In 50 mM glucose and 100 nM insulin challenge;

- No statistically significant results were observed between gene expression.

Future Studies

- Determine the effect of high glucose and insulin in differentiated HT-22 cells and examine over 24 hours and 3-7 days to simulate acute and chronic exposure conditions respectively in hippocampal cells.
- Investigate effects using the anti-diabetic viral protein, E4orf1 and its effect on improving mitochondrial dysfunction in HT-22 cells.

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References


Impact Area

Expanding knowledge in the area of health and wellness as it relates to our better understanding of the association of two medical conditions confined to specific regions of the body. Namely, investigating the potential role of Type 2 Diabetes in the exacerbation of Alzheimer’s disease.