Induction of Glyoxalase 1 as a Strategy to Prevent Methylglyoxal-Induced Insulin Resistance in Rat Cardiomyocytes: Implications for Diabetic Cardiomyopathy

Category: Undergraduate student
Discipline: Population, Health & Wellness

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Background

- Diabetes Mellitus (DM) is one of the major challenges to human health in the 21st century
- Diabetic cardiomyopathy: a long-term complication of DM
- Insulin resistance is associated with diabetic cardiomyopathy
- DM is associated with an increase in methylglyoxal (MG) a highly reactive compound
- MG induces insulin resistance
- MG is detoxified through the glyoxalase system by glyoxalase-1 (Glo-1) enzyme using reduced glutathione (GSH) as co-factor
- Glo-1 expression is increased by trans-Resveratrol (tRES, R) and Hesperetin (HES, H) which are Nrf2 activators (Figure 1)

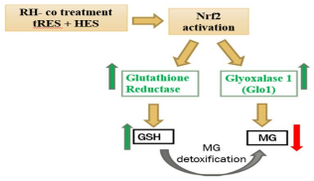

Figure 1: Nrf2 activation by tRES-HES co-treatment

Study Objectives

- Investigate the effect of tRES-HES co-treatment in preventing MG-induced cardiac insulin resistance by evaluating:

a) Glo-1 activity

b) Phosphorylation of Akt and GSK3b

Methods

- **Design**

In vitro laboratory experimental study using H9C2 rat cardiomyocyte cell line

- **Treatment Protocol**

Cells were seeded onto 6-well plates and treated with MG (100uM) +\ - tRES-HES (RH 10uM) for 24 hours. Some cells were stimulated with insulin (100 nM) for 10 minutes

- **Study Experiments**

- Cell viability using Alamar Blue reagent
- Glo1 activity assay
- Protein expression (Akt, GSK3b) *via* Western blotting

- **Statistical Analysis**

- One-way ANOVA and post hoc analysis
- Values represent mean ± SEM; P<0.05

Results

Cell Viability

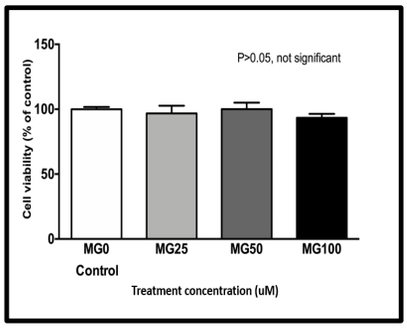

Figure 2: The effect of MG on cardiac cell viability after 24 hours of treatment.

- MG did not affect the cell viability significantly after 24 hours of treatment (P>0.05). Doses beyond 100 uM MG decreased the cell viability below 80%.

Glo-1 Activity

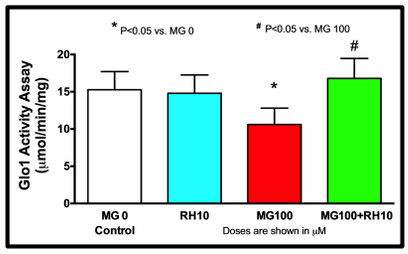

Figure 3: Glo-1 activity in response to MG and tRES-HES co-treatment for 24 hours.

- MG reduced Glo-1 activity (P<0.05)
- RES-HES combination restored Glo-1 activity compared to MG100 uM (0.97±0.05 vs. 0.53±0.06; P<0.05)

Akt Phosphorylation

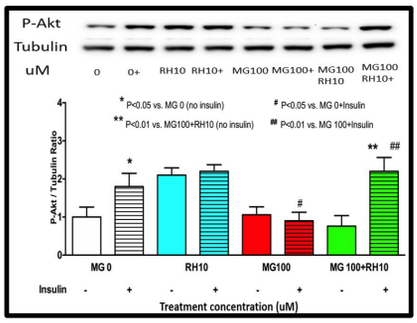

Figure 4: Akt phosphorylation in response to MG and tRES-HES co-treatment for 24 hours.

- RES-HES treatment of cells incubated with MG 100 increased the phosphorylation of Akt in response to insulin compared to cells treated with MG 100 in response to insulin (2.2±0.21 vs. 0.90±0.13; P<0.01)

GSK3b Phosphorylation

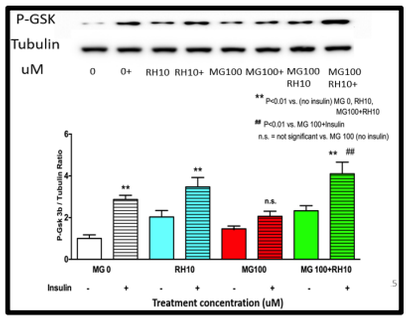

Figure 5: GSK3b phosphorylation in response to MG and tRES-HES co-treatment for 24 hours.

- GSK3b phosphorylation was increased in control cells with insulin (P<0.01)
- RES-HES treatment of cells incubated with MG 100 insulin increased the phosphorylation of GSK3b in response to insulin compared to cells treated with MG 100 + insulin (4.1±0.3 vs. 2.06±0.14; P<0.01)

Conclusions

MG induced cardiac-insulin resistance and a decrease in Glo1 activity was prevented by tRES-HES co-treatment

Future Steps

Use Glo-1 inhibitors to specifically study the role of Glo1 in improving insulin signaling in cardiomyocytes

Acknowledgements

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