Chronic hyperglycemia-induced attenuation of mitochondrial reserve capacity mediates mesangial cell dysfunction in diabetes

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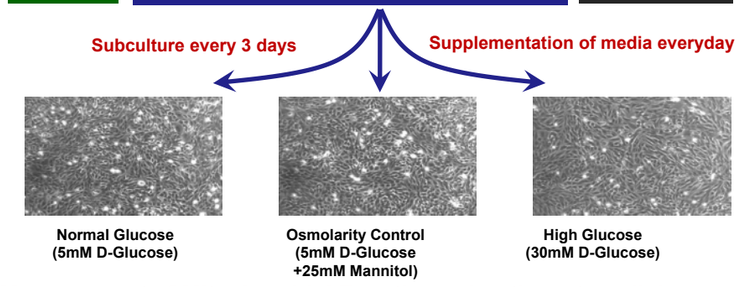
Introduction

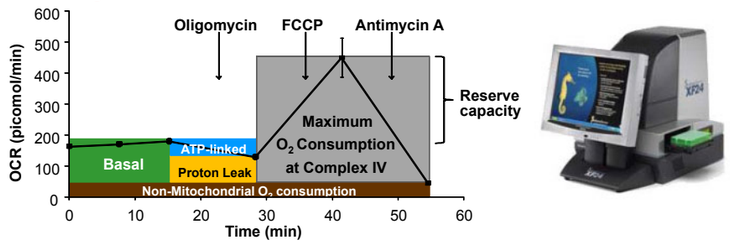
- Chronic hyperglycemia, the primary pathological feature of diabetes mellitus, increases the susceptibility to the development of secondary complications including nephropathy and renal failure.
- Hyperglycemia-induced oxidative stress have been implicated in mesangial cell proliferation, apoptosis, glomerular basement membrane thickening and glomerular dysfunction that are associated with diabetic nephropathy.
- Studies using isolated mitochondria from cells exposed to hyperglycemia and animal models of diabetes have suggested an association between mitochondrial dysfunction and increased oxidative stress in diabetes.
- The changes in mitochondrial function in response to chronic hyperglycemic stress have not been investigated in intact cells. Determination of mitochondrial function in intact cellular environment is important as it maintains the cellular mitochondrial organization and the metabolite flux, critical factors influencing accurate determination of bioenergetic profile and mitochondrial function.
- ***Here we hypothesize that chronic hyperglycemia-mediated inhibition of mitochondrial reserve capacity induces mesangial cell dysfunction in hyperglycemic stress.***

Methods

Chronic hyperglycemic treatment of mesangial cells



Measurement of Mitochondrial Function using the extracellular flux analyzer



Results

Bioenergetic profile of mesangial cells exposed to chronic hyperglycemia

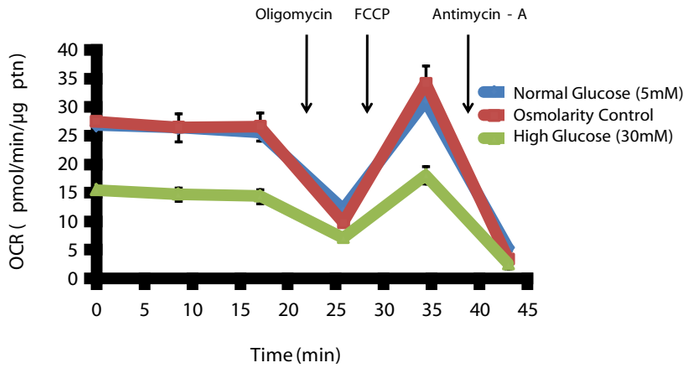


Figure 1. Chronic hyperglycemia alters bioenergetic profile of mesangial cells. Mesangial cells (MES-13) were exposed to 30mM -D-glucose for 14 days. Cellular bioenergetics determined using, the XF24 analyzer (Seahorse Bioscience) demonstrates a significant decrease in bioenergetic capacity of hyperglycemic cells. Average OCR values (n=4-5) normalized to total protein were plotted.

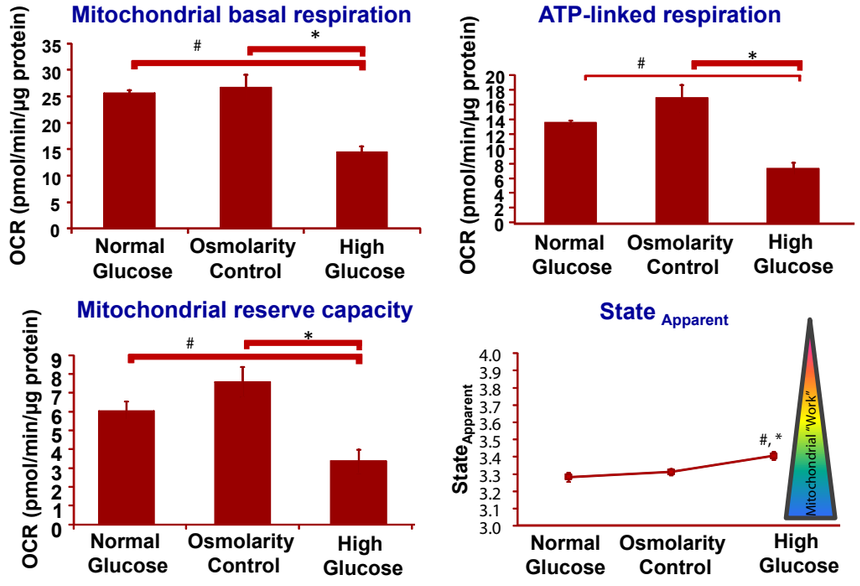


Figure 2. Chronic hyperglycemia decreases basal oxygen consumption rate, ATP-linked respiration, mitochondrial reserve capacity and increases mitochondrial stress of mesangial cells. Average OCR values were analyzed by student t-test. #, * indicates p 0.05 compared to normal glucose and osmolarity control respectively .

Glycolytic rate of mesangial cells exposed to chronic hyperglycemia

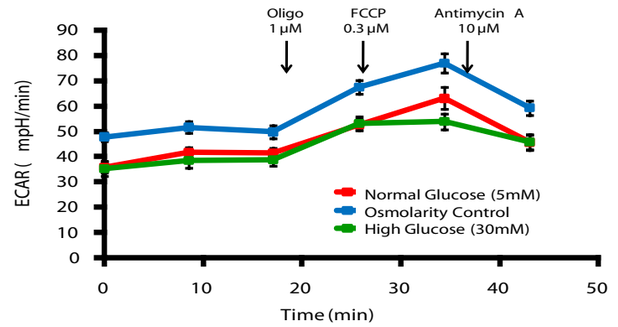


Figure 5. Chronic hyperglycemia does not affect extracellular acidification rate (ECAR) in mesangial cells

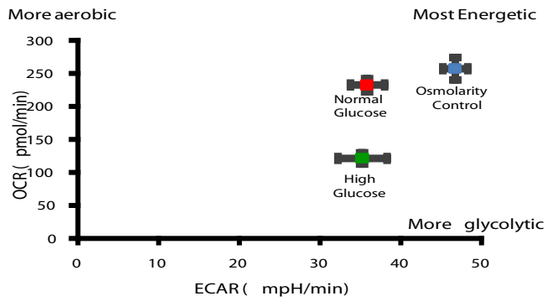


Figure 5. Chronic hyperglycemia decreases mitochondrial energy production without altering cellular glycolytic rate in mesangial cells

Conclusions

- Chronic hyperglycemia alters the bioenergetic profile of intact mesangial cells (MES-13)
- Mitochondrial damage resulting from chronic hyperglycemic treatment inhibits basal mitochondrial respiration, ATP-linked respiration and mitochondrial reserve capacity.
- Chronic hyperglycemia increases mitochondrial stress in mesangial cells (MES-13)
- Cellular glycolytic rate of mesangial cells is unaffected by hyperglycemic treatment for 14 days in culture.
- This study demonstrates that chronic hyperglycemia inhibits mitochondrial function without altering the glycolytic rate in intact cells.

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