2021
August 06
Webinar

29th International Conference on
Clinical Diabetes, Diabetic Medication & Treatment

Mitochondrial integrity is affected by excess cellular glucose influx in the absence of TXNIP

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Chronic high blood glucose level results in detrimental effects on tissues systemically. However, the process by which excess glucose influx leads to damage at the cellular level globally is poorly understood. Our work aims toward understanding the effects excess glucose has on organelles such as mitochondria assessed within an in vivo setting.

TXNIP negatively regulates glucose uptake by directly facilitating GLUT1-4 endocytosis while integrating metabolic and growth factor signals. Because of their unregulated glucose uptake into peripheral tissues, TXNIP KO mice are hypoglycemic. Using TXNIP KO mice as a model of excessive cellular glucose uptake, we examined the glucose effect on mitochondrial function in vivo by examining thermogenesis in brown adipose tissue (BAT). Increased glucose uptake by BAT cells caused a shift of BAT lipid composition in cellular and mitochondrial membranes towards shorter, more saturated lipid forms; this shift subsequently affected mitochondrial integrity under stress, helping explain BAT thermogenesis defects. Additionally, this excess intracellular glucose resulted in reduced expression of fatty acid elongation, PUFA transport, and cardiolipin modification genes, further exacerbating lipid composition change. To further confirm our conjecture, these abnormal lipid phenotypes could be rescued using a ketogenic diet that limits the available peripheral tissue glucose uptake, strongly supporting our theory that changes observed in lipid composition and gene expression are due to excess cellular glucose uptake. Overall, our findings highlight that cellular damage caused by excess glucose influx into tissue cells occurs throughout the body far earlier than is currently defined by symptoms found through clinical diagnosis.