UAEU

جامعة الإمارات العربية المتحدة
United Arab Emirates University

The College of Graduate Studies and the College of Medicine and Health Sciences Cordially Invite You to a

PhD Dissertation Defense

Entitled

High glucose, high fatty acid-induced toxicity, oxidative and metabolic stress and alterations in cell signaling in pancreatic Rin-5F cells: attenuation by N-acetylcysteine

by

Arwa Munassar Ali Thabet Al Nahdi

Faculty Advisor

Prof. Haider Raza, Department of Biochemistry
College of Medicine and Health Sciences

Date & Venue

13:00 PM
Tuesday 19th March 2019
Shaikha Fatima Hall 2C021, 2nd floor
College of Medicine and Health Sciences

Abstract

Background: Hyperglycaemia and hyperlipidaemia are the main causes of diabetes and obesity-associated complications. Increased oxidative stress, inflammatory responses and altered energy metabolism have been associated with hyperglycaemia and hyperlipidaemia. The concept of 'glucolipotoxicity' has arisen from the combination of the deleterious effects of the chronic elevation of levels of glucose and fatty acids on pancreatic β-cells' function and/or survival. The synergistic effect of both nutrients exacerbates β-cells' dysfunction over time and creates a vicious cycle of impaired insulin secretion and metabolic disturbances. Though numerous studies have been conducted in this field, the exact molecular mechanisms and causative factors still need to be established.
Aim: The aim of the present work is to elucidate the molecular mechanisms of altered cell signalling, oxidative and metabolic stress, and inflammatory/antioxidant responses in the presence of high concentrations of glucose/fatty acids in a cell-culture system using an insulin-

secreting pancreatic β-cell line (Rin-5F) and to study the effect of the antioxidant N-acetylcysteine (NAC) on β-cell toxicity.

Study Design: In our study, we investigate the molecular mechanism of cytotoxicity due to high glucose concentration (up to 25mM) and high saturated fatty acid concentration (up to 0.3mM palmitic acid) on Rin-5F cells. In this regard, initially, we investigate the effects of streptozotocin (STZ), a known β-cell toxin that is structurally related to glucose, to identify specific molecular and metabolic targets affected in pancreatic β-cells. Furthermore, we aim to elucidate the cytoprotective effects of NAC on β-cell toxicity induced by STZ/high glucose/high palmitic acid.

Results: Our results show that the cellular and molecular mechanisms of β-cell toxicity are mediated by increased oxidative stress, imbalance of redox homeostasis, disruption of mitochondrial bioenergetics and alterations in cell signalling. On the other hand, NAC treatment attenuates β-cell cytotoxicity, apoptosis and mitochondrial damage associated with oxidative stress.

Significance: The use of an *in-vitro* cell-culture model in this study signifies the cellular and molecular mechanism(s) of β-cell toxicity without the involvement of multiple physiological factors that would be seen *in vivo*, which might contribute to the disease progression.

Keywords: Glucolipotoxicity, Rin-5F, streptozotocin, oxidative stress, mitochondria, N-acetylcysteine.