# Role of the Coenzyme $Q_{10}$ Pathway in Atorvastatin-Mediated Reduction in Insulin Secretion

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## Abstract

**Background**: Atorvastatin is a member of statin family, which is prescribed to lower cholesterol levels in patients with hypercholesterolemia. Atorvastatin lowers cholesterol concentration by inhibiting 3-hyroxy-3-methyl-glutaryl-CoA reductase in cholesterol synthesis pathway. It has been proven that statins also exhibits diabetogenic effects by reducing insulin secretion. However the molecular mechanism of this action is not known. Interestingly, patients treated with statins also showed decrease in coenzyme $Q_{10}$ ($CoQ_{10}$) levels and mitochondrial oxidative phosphorylation. **Objective:** In this study, the effects of atorvastatin on insulin secretion, cholesterol levels, mitochondrial function and the potential role of inhibiting $CoQ_{10}$ synthesis was investigated. **Results:** Atorvastatin decreased mitochondrial respiration, glucose-stimulated insulin secretion and cholesterol synthesis, and increased reactive oxygen species in INS-1 832/13 clonal β-cells. The reduction in mitochondrial respiration was partially rescued by 4-hydroxybenzoate, a precursor of $CoQ_{10}$. Further experiments showed that $CoQ_{10}$ could restore the changes in atorvastatin-induced reduction in insulin secretion; however, 4-hydroxybenzoate had no effect on this. Surprisingly, I discovered that $CoQ_{10}$ prevented the cholesterol reduction associated with atorvastatin. **Conclusion:** I believe that both atorvastatin-induced cholesterol synthesis inhibition and $CoQ_{10}$ reduction are crucial in the β-cell impaired insulin secretion.


## Introduction

- Everyday, **206** Canadians die from cardiovascular disease and stroke.
- The primary cause of cardiovascular disease is atherosclerosis. Eventually these plaques can rupture and the resultant blood clot deprives vital tissues of oxygen.
- Unhealthy blood cholesterol levels is the major risk factor of atherosclerosis.
- Statins are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. They reduce low density lipoproteins levels by ~ **20-45%**.
- Statins have been known to reduce the mortality and morbidity associated with CVD but statin-induced therapy can led to **10% - 46%** increase risk of diabetes

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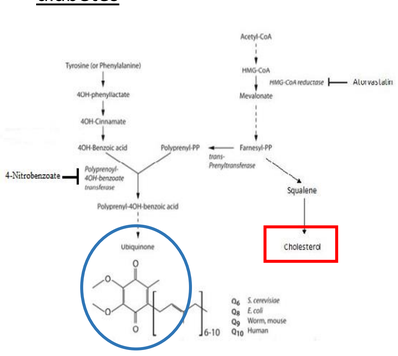
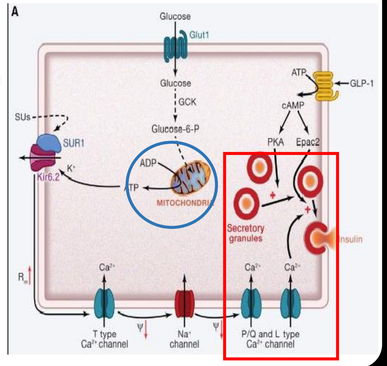
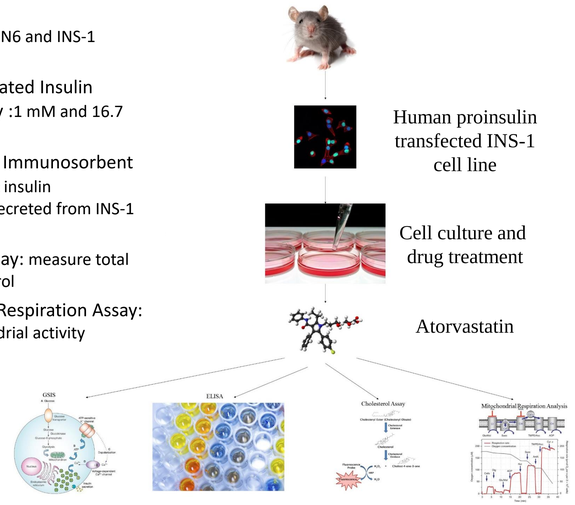



## METHODS

- Cell Culture: MIN6 and INS-1 832/13 cells
- Glucose-Stimulated Insulin Secretion Assay :1 mM and 16.7 mM glucose
- Enzyme-Linked Immunosorbent Assay: measure insulin concentrations secreted from INS-1 832/13 cells
- Cholesterol Assay: measure total cellular cholesterol
- Mitochondrial Respiration Assay: assess mitochondrial activity



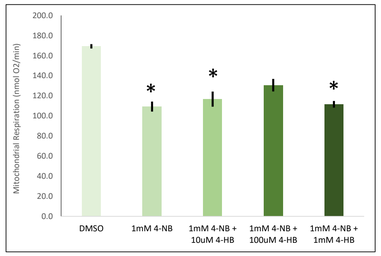




**Figure 1 |** Effects of 4-NB and 4-HB on mitochondrial respiration. Mitochondrial respiration of 10μM, 100 μM and 1 mM of 4-HB with 1 mM 4-NB were measured. It was observed that only 100 μM of 4-HB is able to significantly restore mitochondrial respiration. * $p < 0.05$ compared to DMSO control. † $p < 0.05$ compared to 1 mM 4-NB. n = 4.

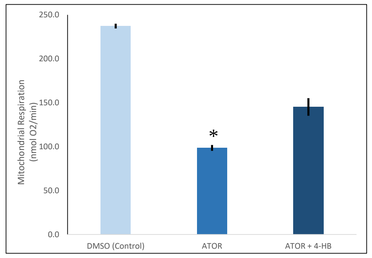



**Figure 2 |** Effect of atorvastatin on mitochondrial respiration. Mitochondrial respiration was measured in atorvastatin (Ator) and atorvastatin + 100 μM of 4-HB treated MIN6 cells. It was observed that atorvastatin significantly reduce mitochondrial respiration. 4-HB partially recued atorvastatin-induced reduction of mitochondrial respiration. * $p < 0.05$ compared to control. n = 5

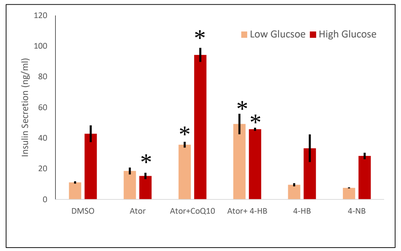



**Figure 3 |** effects of atorvastatin (Ator), atorvastatin + CoQ10 and atorvastatin + 4-HB treatments on insulin secretion of INS-1 cells. Atorvastatin treated INS-1 832/13 cells, showed a significant reduction in insulin secretion at high glucose. CoQ10 restored atorvastatin-induced reduction of insulin secretion, however, the basal insulin secretion in CoQ10 treated cells were much higher than the control group. 4-HB (CoQ10 precursor) was not able to rescue decreased insulin secretion by atorvastatin. 4-HB and 4-NB treated INS-1 832/13 cells did not show any significant difference in insulin secretion compare to DMSO control group. * $p < 0.05$ compared to their respective DMSO group; n = 3.

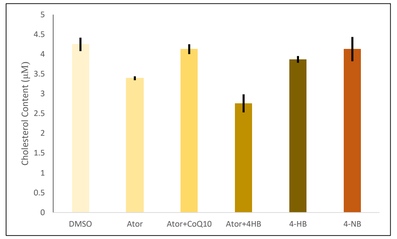



**Figure 4 |** Effects of the atorvastatin, 4-NB and 4-HB on cholesterol levels in INS-1 832/13 cells. Atorvastatin treated INS-1 832/13 cells showed a 21% decrease in cholesterol content, however, this was not statistically significant. Interestingly, CoQ10 restored atorvastatin-induced reduction of cholesterol content, but 4-HB (CoQ10 precursor) reduced it further to 35% reduction of cholesterol content when compared to DMSO control group; n = 3.

## Summary of Results

- Atorvastatin reduces insulin secretion and cholesterol levels
- Atorvastatin impairs mitochondrial respiration
- CoQ10 but not 4-HB can rescue the statin-mediated reduction insulin secretion
- Surprisingly, CoQ10 also increased cholesterol levels in atorvastatin-treated cells to control levels

## Conclusion

- Inhibition of CoQ10 pathway and subsequently mitochondrial dysfunction,is a crucial factor along with reduced cholesterol atorvastatin-mediated insulin secretion reduction.
- These may be the mechanisms associated with statin-induced diabetes.


## Acknowledgment

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