



# Using a GLP-1 Receptor Agonist to Prevent Amyloid Induced Beta Cell Death

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## Abstract

Pancreatic beta cell death is associated with the formation of toxic islet amyloid aggregates. This is seen in both type 2 diabetes and in clinical pancreatic islet transplants for type 1 diabetes. This project investigated the effect of a glucagon-like-peptide-1 receptor agonist, exenatide, on beta cell death and proliferation. Beta cells were cultured with hIAPP, and one group was treated with exenatide to see if the drug would aid beta cell survival. It was determined that treatment with exenatide improves the survival of beta cells.

## Introduction

- Diabetes Mellitus is characterized by chronic hyperglycemia and is classified into two main types, type 1 and type 2<sup>1</sup>
- Type 1 diabetes exhibits a complete insulin deficiency, caused by autoimmune destruction of pancreatic beta cells<sup>1</sup>
- Type 2 diabetes is caused by insulin resistance and eventual failure of pancreatic beta cells<sup>2</sup>
- Islet amyloid polypeptide (IAPP) is a hormone that is stored with insulin in secretory vesicles<sup>3</sup>
- IAPP can aggregate into amyloid fibrils, which are toxic to beta cells<sup>3</sup>
- Deposits of islet amyloid fibrils are commonly found in diabetic patients
- Amyloid deposits are associated with a loss of beta cell mass<sup>3</sup>
- Glucagon-like-peptide-1 receptor agonists are a class of drugs used to treat type 2 diabetes<sup>4</sup>
- They mimic the incretin hormone called glucagon-like-peptide-1 (GLP-1), which stimulates insulin secretion after a meal<sup>4</sup>
- GLP-1 receptor agonists can help manage blood glucose levels in diabetic patients
- They can also decrease pancreatic beta cell apoptosis and increase beta cell proliferation, which are factors that help improve beta cell survival<sup>4</sup>
- Exenatide is one GLP-1 receptor agonist used to treat type 2 diabetes in adults

## Materials and Methods

- Used INS-1 beta cells: a transformed cell line that allows beta cells to replicate
- Untreated control group
- Treatment 1: 10  $\mu$ M synthetic (recombinant) hIAPP
- Treatment 2: 10  $\mu$ M synthetic (recombinant) hIAPP and 10 nM exenatide
- All conditions were cultured for 24 hours
- Insulin/TUNEL immunostaining to detect beta cell apoptosis
- Insulin/PCNA immunostaining to detect beta cell proliferation

## Conclusions

- Beta cell death was significantly reduced in INS-1 beta cells treated with exenatide
- There were far fewer cells undergoing apoptosis in the group of cells treated with hIAPP and exenatide when compared with the cells treated with only exenatide
- Both treatment conditions had more beta cell death than the control, but these results indicate that exenatide improves the survival of beta cells
- Treatment with exenatide tends to increase the proliferation of beta cells
- Beta cells that were treated with hIAPP exhibited more proliferation than those treated with only hIAPP
- The GLP-1 receptor agonist exenatide improves beta cell survival and proliferation
- This is important for preventing the beta cell death that is seen in type 2 diabetes

## Results

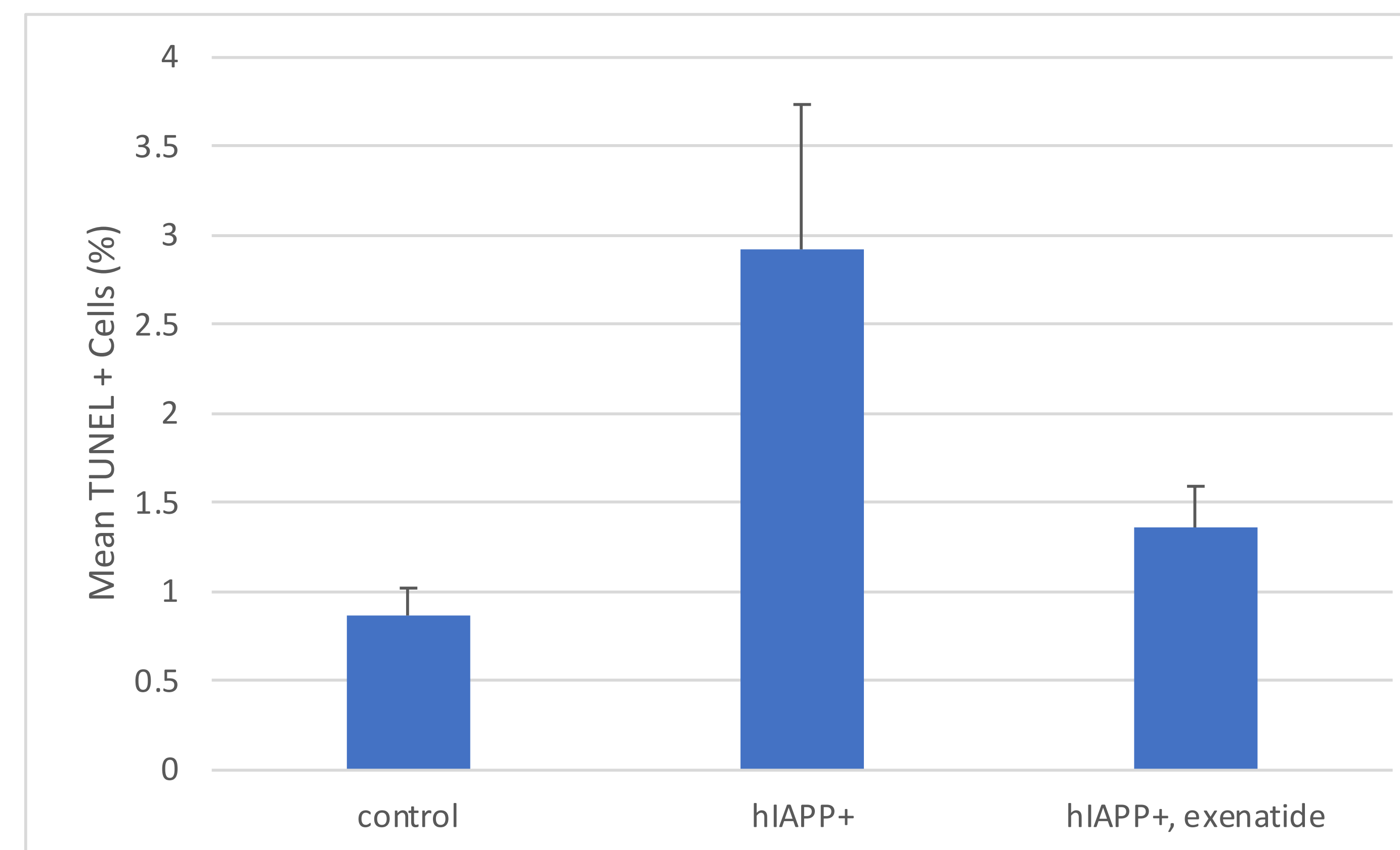


Figure 1. The effects of exenatide on INS-1 beta cell apoptosis. The control beta cells were untreated. Cells in the hIAPP+ group were cultured with 10  $\mu$ M synthetic hIAPP for 24 hours. The hIAPP+, exenatide cells were cultured with 10  $\mu$ M synthetic hIAPP and 10 nm exenatide and cultured for 24 hours.

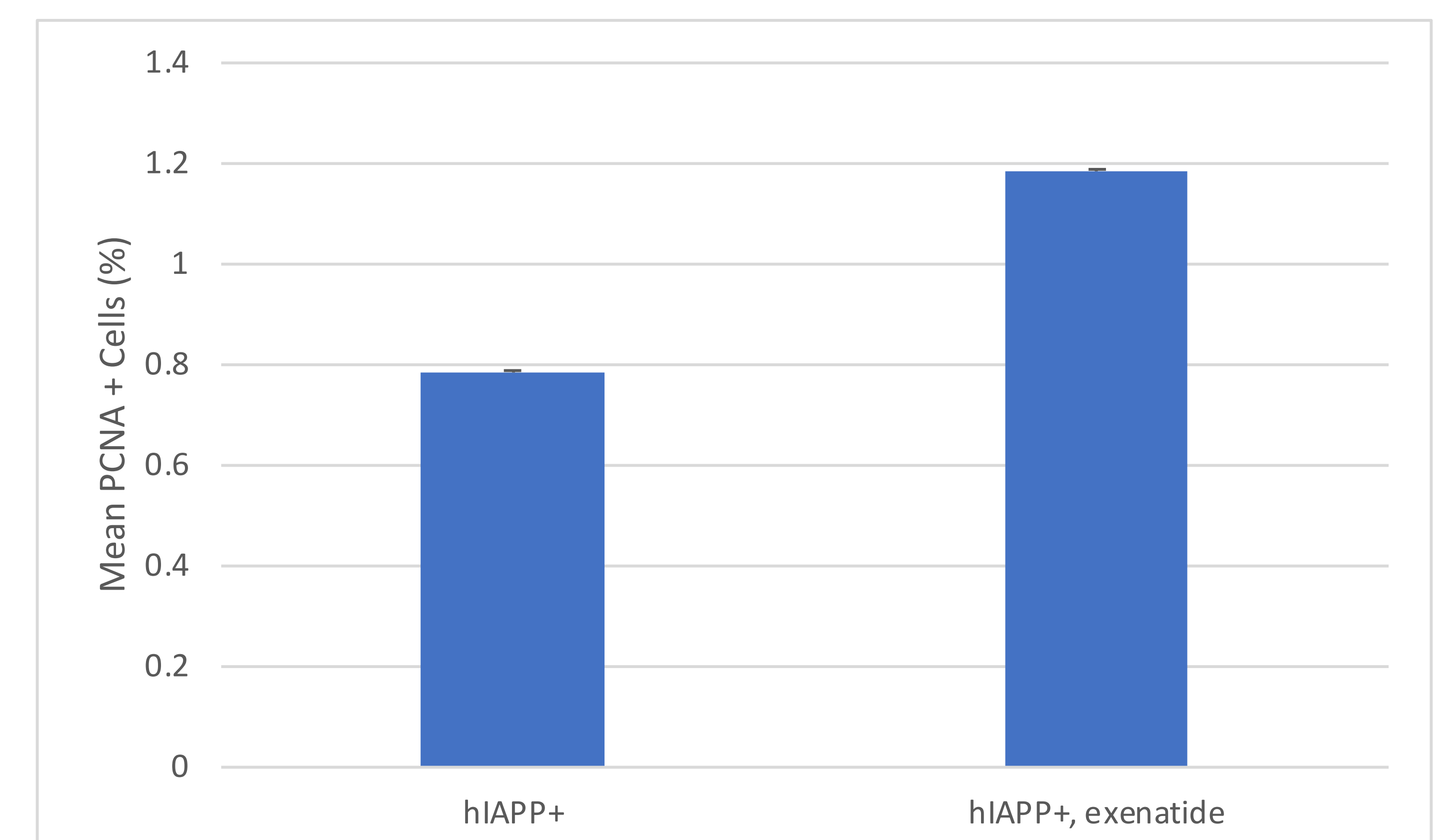


Figure 3. The effects of exenatide on INS-1 beta cell proliferation. Cells in the hIAPP+ group were cultured with 10  $\mu$ M synthetic hIAPP for 24 hours. The hIAPP+, exenatide cells were cultured with 10  $\mu$ M synthetic hIAPP and 10 nm exenatide and cultured for 24 hours.

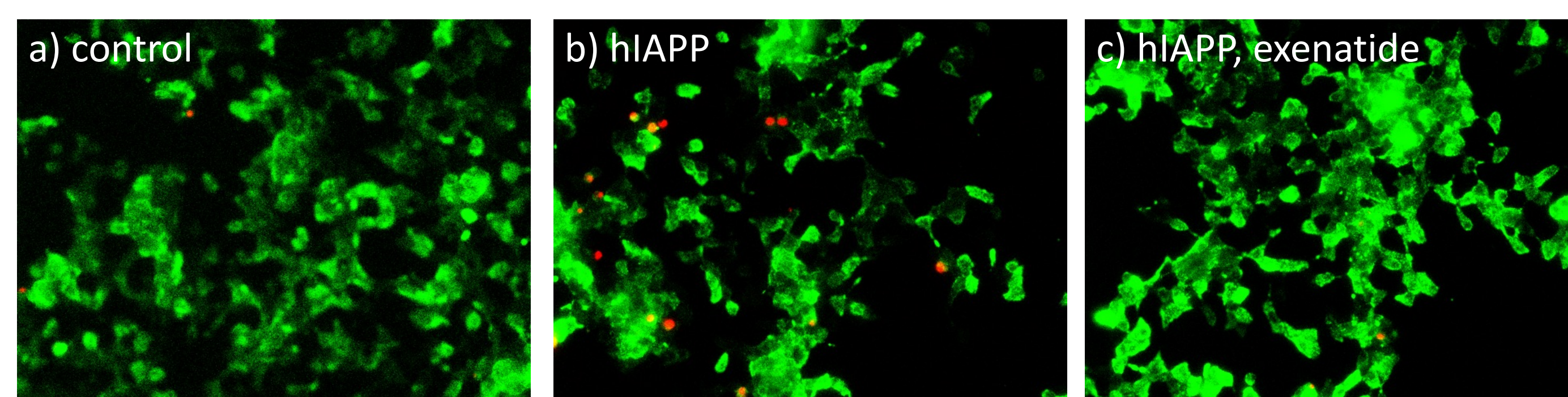


Figure 2 a-c. Treatment with exenatide significantly decreased the number of TUNEL+ beta cells in culture. Immunostaining of INS-1 beta cells for insulin (green) and TUNEL (red).

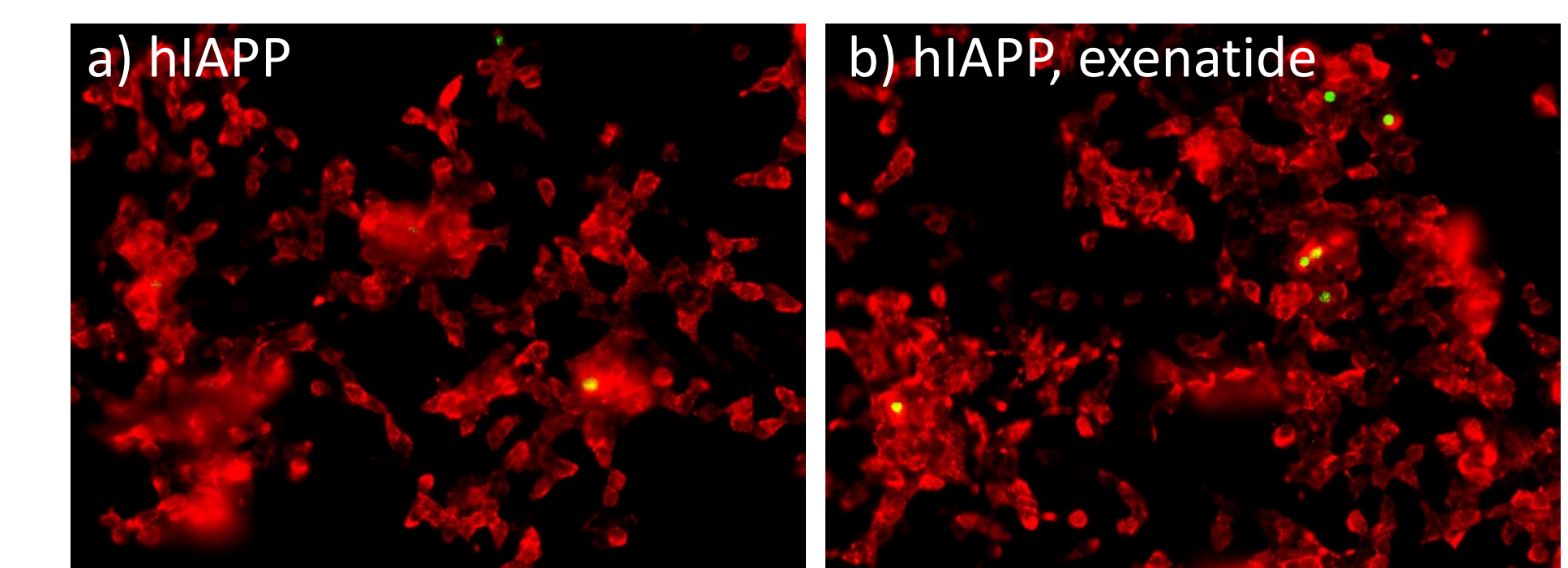


Figure 4 a-b. Treatment with exenatide increased beta cell proliferation in culture. Immunostaining of INS-1 beta cells for insulin (red) and PCNA (green).

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