**The Effect of ER Stress on Beta Cell Proliferation in Diabetics**

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**Abstract**

Beta cells produce insulin to help maintain glucose levels in diabetics. The Endoplasmic Reticulum (ER) found in beta cells helps them produce insulin for the body. When beta cells are overworked, ER stress occurs, which leads to beta cell death. Some beta cells proliferate when they experience ER stress because of the Unfolded Protein Response (UPR). The goal of the study is to determine how the UPR is activated and what factors control it. By finding what factors control it, the UPR could be used to maintain sufficient levels of insulin in diabetics. Samples of beta cells will be exposed to normal and elevated levels of blood glucose levels to activate the UPR. They will be measured for levels of BiP, ATF6, and PCNA and these levels will be compared in normal and elevated glucose levels. BiP, ATF6, and PCNA are byproducts of the UPR being activated and will help determine whether beta cell proliferation occurs in normal or elevated glucose levels. Also, beta cell samples will be exposed to Tg and Tm, agents that activate ER stress. The amount of insulin produced by beta cells in normal and elevated glucose levels will help determine which level of glucose is optimal for UPR activation and beta cell proliferation. Finally, one last test will be analyzing the three pathways that lead to UPR: PERK, IRE1, and ATF6 pathways. All three pathways will be tested for the levels of insulin they produce to determine which pathway has the most influence on UPR. Through this research, some hopes are to gain control of the UPR and to proliferate more beta cells to produce insulin in diabetics when glucose levels are high.

**Introduction**

Endoplasmic Reticulum (ER) Stress is an occurrence in diabetics that hinders beta cell proliferation and ultimately diabetics in general (Papa 2012). Endoplasmic Reticulum Stress occurs when ERs in beta cells are overworked because of the need for insulin in diabetics. Since diabetics have fewer beta cells than non-diabetics, it is much more difficult for them to produce the insulin that they need to remain healthy and maintain consistent glucose levels. This stress ultimately leads to the death of many beta cells, making it even more difficult for diabetics to produce enough insulin to survive. Ultimately, ER stress is detrimental to diabetics because it kills off the few remaining beta cells they have and leaves them with no way to produce insulin.

While many attempts have been made to solve the problem of ER stress in diabetics, many studies have fell short. Eizirk et. l. (2010) attempted to find a way to solve ER stress by looking for ways to produce enough beta cells to produce enough insulin while still dealing with ER stress (Eizirk 2010). They discovered a system called the Unfolded Protein Response (UPR), whichproliferates beta cells when their levels are too low in diabetics, but they couldn’t find how to activate it. Other researchers such as Back et. al. (year) unsuccessfully attempted to find a way to activate the UPR in Type 2 Diabetes. While researchers were able to find the solution, they couldn’t find the equation to get them there.

However, Sharma et. l. (2015) discovered factors that activated the UPR, the PERK, IRE1, and ATF6 pathways in beta cells. Through control of these pathways, they found that it would be possible to activate the UPR, begin beta cell proliferation, and ultimately produce sufficient insulin levels. The effects of the three pathways need to be measured to determine which effect has the strongest control over UPR activation. By preventing expression of two pathways and allowing the expression of the other, one can compare the effects the three have on UPR activation.

While expressing one specific pathway, beta cell proliferation will be measured through insulin levels. Also, to ensure ER stress occurs, levels of Ca2+ will be measured as done in Zhang (2019). Insulin levels will first be measured before the UPR is activated and after ER stress occurs. Then, each pathway will be expressed once in three different beta cells and insulin levels will be measured after UPR activation occurs. The difference in insulin levels before and after UPR activation will indicate which pathway has the most control over the UPR and beta cell proliferation in general.

While there are many studies that revolve around the effect of the UPR on beta cell proliferation in diabetics, by finding the factors that control it, it will be easier to maintain insulin and glucose levels in diabetics. This study focuses more on how to deal with the root of the problem, as other studies have already identified it. The more control we have over a certain cycle, the more control we have over the body. Therefore, we hypothesize that by identifying which pathway has the most control over the UPR, we will be able to use it to maintain insulin and glucose levels in diabetics.

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