The Role of the ERK 1/2 Proteins in Diabetic Cardiomyopathy

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Introduction to ERK 1/2 Proteins

ERK 1 and ERK 2 are protein kinases that regulate both cell regulation and cellular proliferation. Activation of these proteins occurs through phosphorylation within the proteins. Once activated these proteins initiate anti-apoptosis processes increasing the chance of cell survival. Research has demonstrated that increased ERK 1/2 activity lowers the development of high-fat diet induced obesity. (Figure 1). In a similar study ERK 1/2 was also found to decrease heart failure and cardiac pathologies. Specifically this study demonstrated that cardiac contractility and faster relaxation times were evident in those mouse models with elevated ERK 1/2 levels.[1]

Overview of Diabetic Cardiomyopathy

Diabetic cardiomyopathy is a subset of heart disease that is characterized by mitochondrial dysfunction, hypertension and an overall inability of the heart to pump adequately. The causation behind the correlation between the increased rate of development of cardiomyopathy in those individuals afflicted with diabetes is unknown, but abnormal cardiac fuel usage and intracellular lipid accumulation have been suggested. In a diabetic body there is a surplus of fatty acids in the blood as it is used as compensation for the body´s inability to use glucose as fuel, due to the inadequate or complete lack of insulin. This surplus of fatty acid can travel to the heart causing buildups which may lead to cardiomyopathy. These reasons are still being investigated to determine if these diseases are linked physiologically or are caused by similar environmental factors.[4-5]

Apoptosis in Diabetic Cardiomyopathy

Another factor that has been suggested as a correlation to the development of heart failure is an increased level of apoptosis within myocardial cells. Caspase-3 is an enzyme vital in the apoptosis pathway. In prior studies levels of Caspase-3 in mice induced with diabetic cardiomyopathy were investigated to determine any relationship between cardiomyopathy and apoptosis levels. A positive correlation was found demonstrating that apoptosis pathways are indeed elevated in cases of diabetic cardiomyopathy.[3]

Within the same study mitochondrial concentrations were measured within the myocardial tissue. It was found that mitochondrial concentrations were decreased in the tissues with elevated levels of Caspase-3. Specifically the mice induced with diabetic cardiomyopathy via Streptozotocin, demonstrated low levels of mitochondrial saturation. (See figure 3).[3]

This finding further solidifies prior findings that suggest that mitochondrial depletion is an indicator in the development of cardiomyopathy.

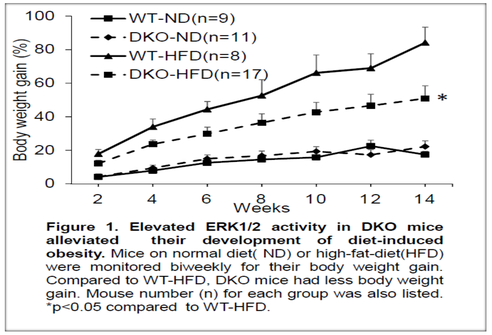

Figure 1. Elevated ERK1/2 activity in DKO mice alleviated their development of diet-induced obesity. Mice on normal diet(ND) or high-fat-diet(HFD) were monitored biweekly for their body weight gain. Compared to WT-HFD, DKO mice had less body weight gain. Mouse number (n) for each group was also listed. *p<0.05 compared to WT-HFD.

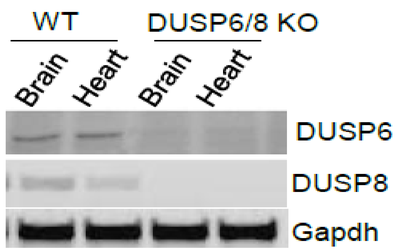

Figure 2: Protein levels of DUSP6 and DUSP8 from brain and heart tissues of the indicated mice

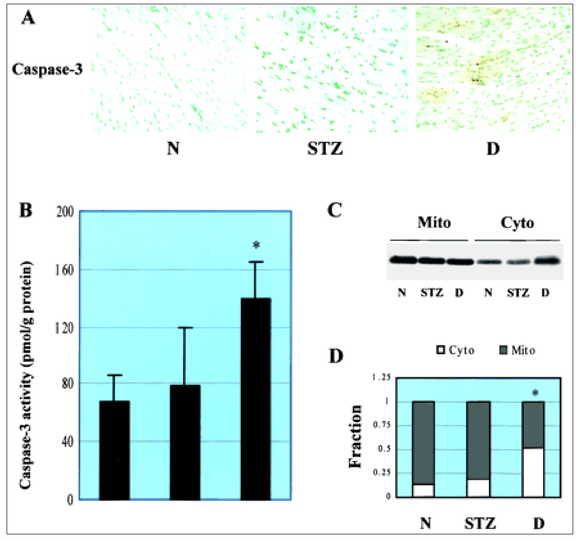

FIG. 3. Detection of caspase-3 and mitochondrial cytochrome *c* release. Activation of caspase-3 was measured by immunohistochemical staining methods (*A*) and enzymatic assay for its activity (*B*), and mitochondrial cytochrome *c* release was measured by Western blotting (*C* and *D*) from the hearts of normal (N), STZ control (STZ), and diabetic (D) mice as described in RESEARCH DESIGN AND METHODS. *D*: The quantitative analysis of cytochrome *c* release from mitochondria into cytosol. *$P < 0.05$ versus control (N).[3]

Aim 1 Goals and Methods

Streptozotocin is widely used drug to induce diabetes in small animals. Streptozotocin kills the beta cells within the pancreas, which are the main source of insulin in the body. The drug accomplishes this killing via interruption of DNA structure through alkylation as well as through the creation of toxic chemicals such as hydrogen peroxide and nitric acid.

The first aim of this study will be to induce diabetes in both wild type and DUSP 6/8 knockout mice. (These mice are from strains that have already been genetically altered to remove DUSP6/8 genes, see Figure 2).[1] This will be done by injecting the mice with Streptozotocin five days consecutively through via intraperitoneal injection techniques. Glucose levels will be monitored before injection and two weeks after injection to determine if diabetes is induced in the mice.[6-8]

Aim 2 Goals and Methods

The main goal of this study is to determine if DUPS 6/8 knockout mice are protected from diabetic cardiomyopathy. Following the process of Streptozotocin injection described in aim 1 those mice who develop diabetes (determined through the measurement of glucose levels) will be chosen to assess cardiac function 12 weeks following injection.

To assess cardiac function Brain Natriuretic Peptide, Troponin and mitochondrial saturation levels will be determined. Brain Natriuretic Peptide levels are increased significantly during heart failure. High cardiac output which is often associated with cardiomyopathy causes for an increase in Brain Natriuretic Peptide and is a reliable method of determining heart failure.[2] Troponin is a protein found in cardiac and skeletal muscle and is vital for contraction control. When the heart muscle is injured Troponin is released in the blood and can be directly measured as an indicator of cardiomyopathy.[2] Finally, mitochondria are vital to ATP creation within the cell that allow for effective contraction. Mitochondrial dysfunction has been shown to be directly related to cardiomyopathy as the heart is no longer able to properly function when ATP is depleted. In order to test the activity of mitochondria within the heart oxygen consumption rates can be measured as the mitochondria generates ATP using aerobic respiration. Measuring the exact saturation of mitochondria can also be measured using biomarkers as identifiers.[3]

References

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