Link found between the CYP2D6 enzyme and neuropathy (T2D4) in diabetes patients: Possible target of therapy?

Authors: William Guzman Melissa Hughes Laura Taylor Danielle Davis Sean Williams

Published Date: 11-09-2014

University of Arkansas

School of Mathematics

In patients with type 2 diabetes and neuropathy, investigators have determined that changes in the homology and function of genes (either the homology or gene functions) are likely to be occurring. The potential relevance of this information is not yet known. This is according to a recent study by Lori Strader, M.D., and colleagues from the Department of Pharmacology and Experimental Therapeutics at the University of Texas Health Science Center at Houston (UTHealth), Houston, Texas.

Both of these diseases, type 2 diabetes and neuropathy, are closely related. A few decades ago the mechanism of how the body takes in and breaks down blood glucose through its fat cells was not well understood.

As fat cells release glucose to the blood to be used for energy, the net movement of glucose from the adipose tissue to the blood is called the uptake and conversion to energy, or the power plant. Homology (protein code) plays a critical role in the uptake and conversion of blood glucose.

In patients with type 2 diabetes and neuropathy, some patients find that their blood glucose level goes up while others do not. When this happens, this is called hyperglycemia. Increased blood glucose level suggests disease progression with increased risk of weight gain, obesity, increased cholesterol, and elevated blood pressure, among other factors.

Several years ago, researchers used a combination of fasting blood glucose and body weight to determine what happened to patients after they stopped taking the oral drug metformin. They were able to find that during the fasting period, some patients become obese and others develop type 2 diabetes. They also discovered that the blocking of the CYP2D6 enzyme or its receptor in the HPA axis (the way the cells control glucose), has anti-diabetic effects.

The researchers also determined that evidence of the presence of the CYP2D6 enzyme or its receptor in the blood indicates a protective effect on blood glucose levels during the fasting period.

To determine if this enzyme was indeed present, they started using two types of drugs: called monoclonal antibodies to CYP2D6, which induced CYP2D6 in the blood or to a different cell receptor, the P1R3C9.

As expected, the former molecule led to CYP2D6 making in the bloodstream. However, the P1R3C9 molecule did not.

Further investigation revealed that a specific peptide called HD-1, produced in the pancreatic cells as a response to the inhibition of CYP2D6, did not exist in patients with type 2 diabetes.

Consequently, the researchers believed that there was a connection between CYP2D6 and the hyrophilization activity of the immune cells (like macrophages) in the pancreas.

They then tested plasma levels of a number of peptides. The main peptide that affected blood glucose levels in patients with type 2 diabetes and neuropathy was a peptide called BB1.

In addition, researchers observed an increase in binding between the messenger RNA (a unique molecule associated with peptides) and the peptide. This phosphorylation of BB1 caused a degradation of the CYP2D6. They believe that this degradation is a significant development and indicates that the activation of BB1 is a response to the inhibition of CYP2D6.

In addition, according to the researchers, the beta cell proliferation responses of the immune cells are greatly enhanced in patients with diabetes. In this particular case, that effect was also seen in patients with neuropathy, the result of the loss of parasympathetic nerve cells.

According to the researchers, these findings have profound implications for type 2 diabetes research. They intend to further develop the study to find out if the bp2d6 peptide blocks platelet dysfunction. For those patients with neuropathy, data have shown that any possible therapy for managing the loss of parasympathetic nerve cells may be reduced with the activity of the BB1 protein.

The researchers have given the epilepsy team in the UTHealth Department of Neurology with this research. They were able to replicate these findings in rodent models of neuropathy.

A Yellow And Black Bird Is Standing On The Ground