Diabetes

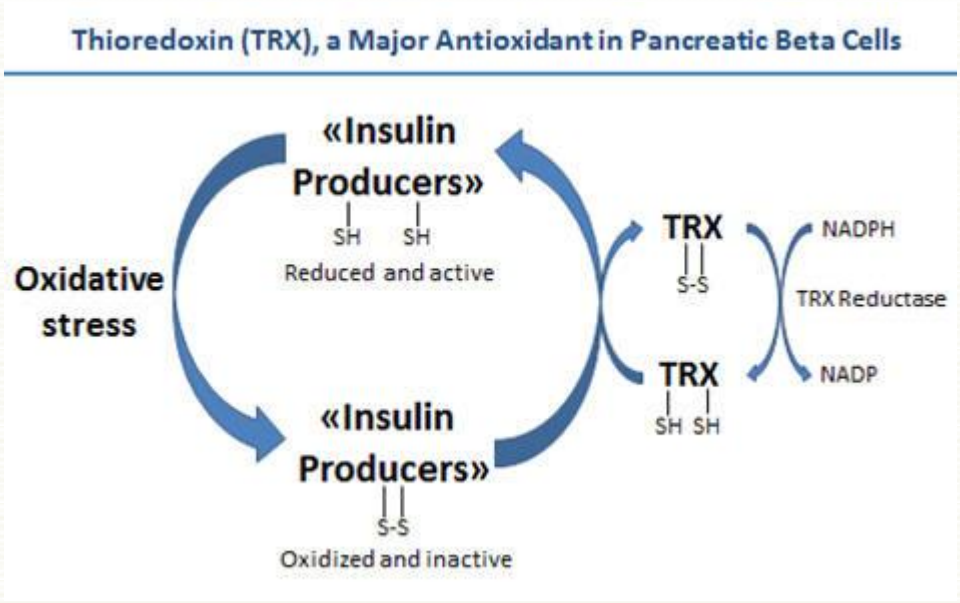
Normally, control over metabolism is so automatic that we give it no thought. However, this extremely demanding process evolves coordination of many hormones and metabolic factors. One of the most essential factors is insulin, a little peptide produced in the beta cells of the pancreas. Damage or loss of these "insulin factories" gives rise to the metabolic situations we group together under the name "diabetes". The health problems which arise in diabetes are complex and many factors are involved.

The extent of diabetes is unbelievable! It is estimated that, world-wide, 375,000,000 people suffered from this disease. Click here for more information). In the USA; over 9% of the population had diabetes in 2012 and the total costs of the disease were estimated to be $245 billion (Click here for more information).

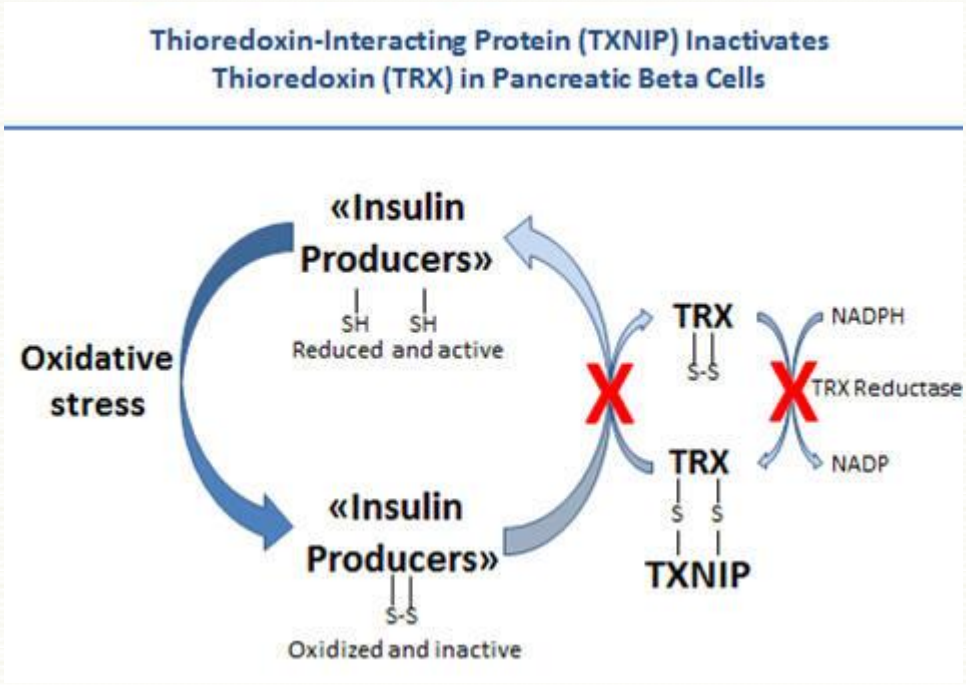
Clearly, an affordable cure for diabetes should be a major goal for medicine. Perhaps this is now possible...

A New Approach to Diabetes Research and a Possible “Cure” for Diabetes

Loss of beta-cell mass is a major factor in the development of both type 1 and type 2 diabetes. This process, apoptosis or “programmed cell-death”, is initiated by oxidative stress. Note that oxidative stress is a real part of our daily life and our "built-in" defense mechanisms are essential for good health. The pancreatic beta cell is especially sensitive to oxidation and is normally protected by the active anti-oxidation protein pair thioredoxin and thioredoxin reductase. These enzymes transfer electrons from NADPH to various proteins of the cell interior and maintain a proper redox balance and stabilize insulin synthesis and release. Synthesis of NADPH from NADP is a normal physiological process which is coupled to the so-called hexose-monophosphate shunt.



A regulatory protein controlling TRX activity (TXNIP) was discovered in 1994 by K.S. Chen and H. F. DeLuca (BBA 1994;1219:26-32). The gene responsible for initiation of TXNIP production is strongly activated by glucose. TXNIP binds to TRX through formation of disulfide bonds, trapping the sulfhydryl groups that otherwise could have been used to reduce oxidized cellular proteins.



Thioredoxin-reacting protein (TXNIP) is found in many tissues in a variety of animals. In the pancreatic beta cell, excessive TXNIP can lead to an imbalance between oxidative stress and recovery through reduction of the resulting protein disulfide bonds. Inhibition of TRX leads to an accumulation of oxidized proteins, reduced insulin synthesis and secretion and apoptosis (programmed cell death). The resulting reduction in beta cell mass is directly

associated with development of diabetes. It has been suggested that TXNIP is the cause of reduced insulin sensitivity in skeletal muscle, which is characteristic of type 2 diabetes.

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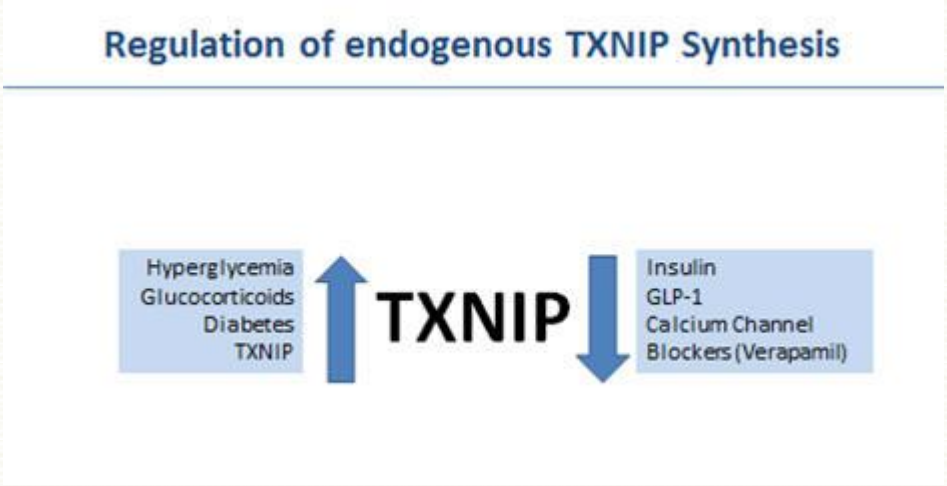
Surprisingly, TXNIP synthesis is stimulated by hyperglycemia and low insulin levels and is self-stimulating, that is, there is positive feedback mechanism controlling TXNIP synthesis. This "vicious cycle" leads to a profound fall in insulin synthesis and to the diabetic state.



A "new" treatment and a "cure" for diabetes?

As you will note from the preceding figure, TXNIP expression and levels fall when animals are treated with insulin, GLP-1 (Glucagon-like protein 1) or Ca^{++} -channel blockers. The latter was observed by a research group looking for effects of these blockers on insulin secretion (G. Xu, J. Chen, G. Jing, and A. Shalev; Diabetes 2012; 61(4): 848-856). One expected that Ca^{++} channel blockers would reduce insulin secretion, since this is Ca^{++} dependent. However, they observed that Verapamil increased insulin release and this was found to be due to partial blocking of TXNIP synthesis. Furthermore, it was observed that Verapamil only reduced the excess TXNIP formed in the presence of hyperglycemia. It had no effect on TXNIP synthesis at normal glucose levels.

Verapamil is an "old" and well-documented, inexpensive antihypertensive drug. When given orally to mice, it reduced TXNIP synthesis and beta cell apoptosis, enhanced endogenous insulin levels and "rescued mice from STZ-induced diabetes". For a recent review see Minireview: Anath Shalev, Molecular Endocrinology 28: 1211-1220, 2014. Clinical studies of verapamil in control of diabetes are in progress. The results will be extremely interesting!