A new understanding of the mechanism of action of insulin sensitizing drugs provides insight into treating metabolic disease

It has been known for some time that there is a connection between diabetes and other diseases that increase with age, including important neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Interestingly, all of these diseases are associated with what is called "insulin resistance", or the reduced response of the body's tissues to the hormone insulin. Moreover, an anti-diabetic compound, pioglitazone, which is a thiazolidinedione (TZD) "insulin sensitizer" that allows insulin to work more effectively on cells, has significantly positive effects in a number of diseases in addition to diabetes. We recently summarized studies that suggest that a new understanding of how the TZDs work provides an important clue as to why these connections exists, and how we can take advantage of this information to produce new therapeutic agents.

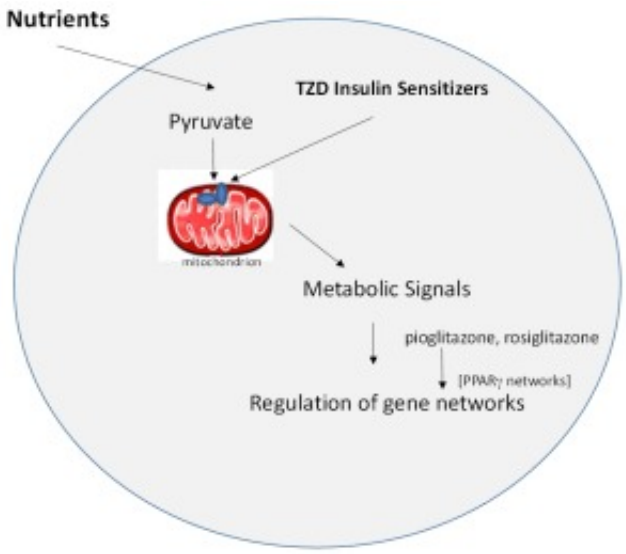

Fig. 1.

TZD insulin sensitizers were discovered over 30 years ago and their mechanism of action has never been completely understood. Over the years, researchers found that the TZDs were able to activate a particular set of genes in fat. The first generation compounds, such as rosiglitazone and pioglitazone, could directly bind to, and activate a key transcription factor in the nucleus of fat cells. The direct activation was a key component of the ability to switch on these genes. Unfortunately, the direct activation of these genes through this interaction also gave rise to important side effects, including retention of water and increased weight gain, all of which limited the use of these drugs. In spite of considerable research by pharmaceutical companies, no one was able to successfully

develop new agents with this mechanism. The new understanding explains why the pharmacology the TZDs is broader than could be explained by just the PPARg network of genes and, most importantly, how the issue of the side effects can be addressed.

We have recently found that the TZDs bind directly to a protein complex in the inner membrane of the mitochondria, the small organelles in each cell that carry out oxidative metabolism. Importantly, this complex in the mitochondria contains recently identified proteins that comprise a route through which pyruvate, an intermediate at the crossroads of metabolism, enters the mitochondria. The effect of the TZDs is to modify the entry of pyruvate at this site and this adjustment affects the metabolism of other nutrients. These modifications, in turn, result in signals that coordinate changes in cell function to match the perceived availability of nutrients. This includes regulation of the expression of gene networks specific for that cell. Thus, fitting with all available data, over-nutrition predisposes to insulin resistance and favors progression of the diseases associated with insulin resistance. Insulin sensitizers are able to counter this metabolic dysfunction.

As can be seen in Figure 1, the gene networks that are regulated by these metabolic pathways include those that are also controlled by the transcription factor PPARg. The original TZDs were able to directly bind to and activate this regulatory protein, thereby driving the unwanted side effects of these, otherwise, effective drugs. New molecules which have been designed to retain the mitochondrial activity, and have a reduced ability to bind to PPARg, have been shown to work in clinical trials with less side effects. Of this new class of TZDs, known as mTOT (for mitochondrial target of TZDs) modulators, one compound is entering clinical trials for fatty liver disease and another is in trials for Alzheimer’s disease.

This new understanding of these metabolic connections may aid in the treatment of some our more costly diseases.

Publication

The TZD insulin sensitizer clue provides a new route into diabetes drug discovery.
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