COMMENTS

Prevention of Diabetes by Inhibition of Tyrosine Phosphatases

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The increased incidence of obesity in recent decades is predicted to be followed by a corresponding increase in incidence of Type II diabetes (1). Recent estimates predict that one-third of children born in 2000 will develop diabetes in their lifetime (2). Type II diabetes was once principally a disease affecting adults, but it has recently become a significant health problem for children also, and the incidence of diabetes in children is expected to increased unless preventative interventions can be developed (3, 4).

Current therapies for diabetes focus on enhancing insulin secretion and improving insulin sensitivity (5). The targets of these treatments are well removed from the initial events in insulin signaling. The manuscript by Winter *et al.* (6), selected for the Best Paper Award in the Experimental Biology Category for 2005, characterizes a therapeutic compound that has effects on insulin signaling that are more direct. Their strategy targets the insulin receptor itself.

When insulin binds to the α-subunit of the insulin receptor, it disinhibits the tyrosine kinase activity of the β-subunit of the insulin receptor (7). Although the insulin receptor phosphorylates other substrates to propagate insulin signaling, it also phosphorylates itself to further enhance its tyrosine kinase activity. Phosphotyrosine phosphatases (PTP), particularly PTP1B, reduce the degree of phosphorylation of the insulin receptor, which decreases insulin signaling and insulin sensitivity. Vanadium compounds have been known to mimic the effects of insulin by inhibition of tyrosine phosphatases. The vanadium compound bis(maltolato)oxovanadium(IV) (BMOV) was used to improve insulin sensitivity.

The effect of BMOV on insulin signaling was demonstrated by treating rats with insulin, BMOV, or both. Skeletal muscle extracts showed a 1.6-fold increase in phosphorylation of insulin receptors, and insulin showed a 4-fold increase. Insulin and BMOV acted synergistically to induce a 10-fold increase in phosphorylation of the insulin receptor.

To determine the effects of BMOV *in vivo*, BMOV was compared with rosiglitazone, which improves insulin sensitivity by effecting transcription of genes for glucose use. Although rosiglitazone is effective in reducing hyperglycemia, it is associated with increased appetite and increased weight gain. Both rosiglitazone and BMOV prevented hyperglycemia in fatty rats and improved insulin sensitivity. BMOV-treated rats maintained low levels of adiponectin, a marker for insulin resistance, whereas adiponectin increased 4-fold in rosiglitazone-treated animals. These data suggest that BMOV is as effective as rosiglitazone in the prevention of insulin resistance and may have a broader effect on other markers of insulin resistance.

The effects of BMOV and rosiglitazone on food intake and body weight of fatty rats differed markedly. Food and water intake increased in control fatty rats and in rosiglitazone-treated rats. Rosiglitazone-treated rats also gained a larger amount of body weight. In contrast, BMOV-treated rats had food and water intake similar to lean control rats, which indicates that BMOV prevented the polydipsia associated with hyperglycemia and also inhibited the development of hyperphagia and weight gain that are

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exacerbated by rosiglitazone. The inhibition of hyperphagia and weight gain could be a significant advantage for a phosphotyrosine inhibitor over rosiglitazone.

This work elucidates a strategy to block the development of insulin resistance at the insulin receptor itself rather than targeting points that are more distal in the insulin-signaling pathway. Others have suggested that PTPB1 would be a useful target for treatment of diabetes. This paper provides a proof of this principle, and suggests that this strategy may have significant advantages over other strategies that target events that are more distal in the insulin-signaling pathways. Because BMOV is a general inhibitor of tyrosine phosphatases, more-specific phosphatase inhibitors may be required to provide safe and effective prevention of diabetes.

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