Oral Vanadium and Lowering of Blood Glucose

As one of a number of laboratories worldwide that is intensively investigating the potential of vanadium compounds as therapeutic agents in diabetes, we take exception to the implications of the recent article of Malabu et al. (1). In our laboratory and others, oral vanadium treatment results in plasma glucose lowering along with amelioration of other diabetes symptomatology (2,3).

The dose of vanadium used by Malabu et al. (1) is far lower than the therapeutic dose generally used in our laboratories (between 75 and 100 $mg \cdot kg^{-1} \cdot day^{-1}$ of vanadyl sulfate), which leads us to wonder how they obtained any therapeutic effect at all. Blondel et al. (4) reported daily vanadium intake for diabetic rats treated with sodium metavanadate (0.20 mg/ml) as 5 mg/day, substantially more than the 1 mg/day used by Malabu et al. (1), and almost surely subtherapeutic. The long onset of action may have been indicative of time required for tissue vanadium accumulation.

Lowering blood glucose levels by undernourishment is qualitatively different from treating diabetes with a therapeutic agent such as vanadium (5). Untreated streptozocin (STZ)-induced diabetic rats (55 mg/kg) that were pair-fed with vanadyl-treated diabetic rats did not show improved glucose kinetics during submaximal hyperinsulinemic clamps, indicating that food restriction, in contrast to vanadyl treatment, lowered plasma glucose without improving glucose uptake and metabolism (6). Food restriction in pair-fed *fa/fa* rats also did not improve glucose tolerance, while vanadate treatment did (7). In BB rats, vanadyl sulfate treatment lowered insulin requirements, further underscoring the insulin replacement value of vanadium compounds (8).

The authors' contention that plasma or tissue vanadate concentrations have not been systematically studied in diabetic rats is no longer true. Mongold et al. (9) reported vanadium levels in a variety of tissues in response to vanadyl sulfate administration at a number of different concentrations, along with daily fluid intakes. Meyerovitch et al. (10) reported plasma vanadium concentrations, vanadium intake, and fluid intake in rats, as well. A detailed investigation of the relationship between daily vanadium intake, plasma and kidney vanadium levels, and plasma glucose levels in individually housed diabetic rats has recently appeared (11).

Malabu et al. (1) described listlessness and lack of appetite as one of the consequences of gavaging with vanadate. This contrasts with another investigation in which sodium metavanadate was given by gavage at concentrations up to 20 $mg \cdot kg^{-1} \cdot day^{-1}$ for 28 days, with no significant decrease in food intake (12).

Thus, the authors' claim that the effect of vanadate in reducing glycemia is the same as the effect of food restriction ignores the fact that animals with the same plasma glucose levels may yet be more severely glucose intolerant and insulin resistant.

Vanadate treatment of STZ-induced diabetic rats partially normalized diabetes-induced changes in 3-*O*-methylglucose transport (13), suggesting an alternative mechanism for hypophagia to that proposed by the authors. We note that Malabu et al. (1) did call attention to the possibility that an "increase in tissue sensitivity to insulin" may be responsible for the fall in blood glucose levels, which contradicts their statement that "the glycemic fall induced by vanadate ... can ... be attributed entirely to the reduction in food intake."

In conclusion, many lines of evidence lead to an interpretation of the results of Malabu et al. (1) that is consistent with a mechanism for glucose lowering by vanadium treatment entirely distinct from that entailed by food restriction. The discrepancies between these results and previous reports of the effects of vanadium (in the drinking water or by gavage) on food intake in diabetic rats were inadequately addressed in the cited article. Their inclusion would most certainly lead to a different overall summary of the available evidence.

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